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Fetal heart rate and movement patterns in growth retardation

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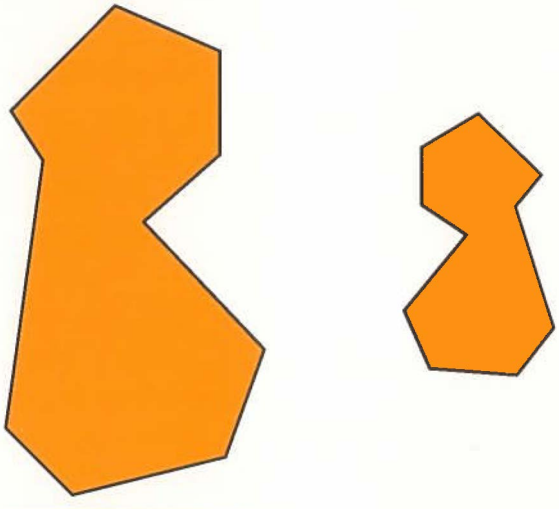
FETAL HEART RATE AND MOVEMENT PATTERNS IN GROWTH RETARDATION



D.J. BEKEDAM

FETAL HEART RATE AND MOVEMENT PATTERNS IN GROWTH RETARDATION

Stellingen behorende bij het Proefschrift van D.J. Bekedam, getiteld:

"FETAL HEART RATE AND MOVEMENT PATTERNS IN GROWTH RETARDATION"

Groningen, 13 december 1989

1. Het antepartum cardiotocogram is pas afwijkend wanneer er sprake is van foetale hypoxaemie.

2. Foetale bewegingen en hartaktie-variabiliteit zijn gerelateerd aan de foetale oxygenatie.

3. Hoewel toediening van zuurstof aan de zwangere leidt tot toename van de foetale pO2, dient de klinische relevantie van langdurige hyperoxygenatie bij dreigende foetale nood nog onderzocht te worden.

4. Acceleraties van de foetale hartfrequentie van meer dan 10 slagen per minuut zijn vòòr een zwangerschapsduur van 35 weken representatiever voor een goede foetale conditie dan acceleraties, die voldoen aan de gebruikelijk gehanteerde norm van 15 slagen per minuut.

5. Doppler-bloedstroomprofielen van de arteriae umbilicales van foetussen met een congenitale en/of chromosomale afwijking zijn niet normaal in ongeveer 50% van deze gevallen. (Meizner et al. Prenatal Diagnosis 1987;7:491.)

6. De verlenging van de duur van de opleiding tot gynaecoloog van 5 tot 6 jaar, heeft op basis van oneigenlijke argumenten plaatsgevonden.

7. De kwantitatieve bepaling van HCG in serum is noodzakelijk om overbehandeling van extra-uteriene graviditeiten te voorkomen.

8. Bij acute of sub-acute pijn en een palpabele afwijking in het kleine bekken dient ook bij het prepuberale meisje gedacht te worden aan een torsie van het ovarium.

9. Computer-analyse van het foetale cardiotocogram is superieur aan de visuele beoordeling; de "expert" weet echter beter.

10. De menselijke foetus is geen schaap.

11. Het onderscheiden van symmetrische en asymmetrische groeivertraging vòòr een zwangerschapsduur van 32 weken suggereert een indeling naar etiologie, die niet hard gemaakt kan worden.

12. Het dagelijks tellen van kindsbewegingen door de zwangere heeft geen grotere voorspellende waarde voor intrauteriene sterfte dan het "terloops" informeren door de verloskundige of de baby goed beweegt. (Grant et al. Lancet,1989 ii:345)

13. Het afbreken van de Berlijnse Muur betekent niet dat het kapitalisme gezegevierd heeft.

14. Het buitenspel zetten van D66 bij de samenstelling van het huidige kabinet heeft geleid tot een bloedeloos gelijkspel.

15. Het vinden van drukfouten in drukproeven geeft dezelfde sensatie als het uitdrukken van meeeters.

16. Thuis bevalt best.

RIJKSUNIVERSITEIT GRONINGEN

FETAL HEART RATE AND MOVEMENT PATTERNS IN GROWTH RETARDATION

PROEFSCHRIFT

TER VERKRIJGING VAN HET DOCTORAAT IN DE GENEESKUNDE
AAN DE RIJKSUNIVERSITEIT GRONINGEN
OP GEZAG VAN DE RECTOR MAGNIFICUS DR. L.J. ENGELS
IN HET OPENBAAR TE VERDEDIGEN OP WOENSDAG 13 DECEMBER 1989
DES NAMIDDAGS TE 4.00 UUR

door

DERK JAN BEKEDAM

GEBOREN OP 15 DECEMBER 1952
TE DJEMBER, INDONESIE

1989

Promotores: Prof. Dr. G.H.A. Visser
Prof. Dr. H.F.R. Prechtl
Prof. Dr. H.J. Huisjes

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tastend aan grenzen
aan vliezen die je scheiden
van ander tasten

luister dat seinen
er is een constant seinen
wezen aan wezen

alle ding is teken
boodschap van dat ander land
waar ik woont en droomt

je hoort het suizen
er is een betekenis
het is niet zegbaar

je mag mij niet verliezen

(naar J.C. van Schagen, "Ik ga maar en ben".)

CONTENTS

1

INTRODUCTION

Intrauterine growth retardation (IUGR) has only been recognized as distinct and clinically relevant phenomenon since the early sixties. Clinicians, until then, thought that babies were small because they had insufficient time to grow. Subsequently, all babies with a birth weight below 2500 grams were called "premature" (WHO 1948).

In 1963, Gruenwald's study on reduced uteroplacental circulation, led to the concept of "fetal deprivation" and to the identification of newborns who were "small-for-gestational age" (SGA).[5] Presently, SGA and IUGR are casually interchanged. However, there is little doubt that they are not identical. This is due to the lack of an independent definition of fetal growth restriction. So far, SGA has been defined in terms of a birth weight below a certain limit, corrected for gestational age, sex and parity. The limit is defined in terms of percentiles or standard deviations below the mean.[1,22] Definition by means of arbitrarily chosen cut-off points on the intrauterine growth curves, is at least doubtful and is caused by a lack of understanding of the pathophysiology of growth restriction of the SGA fetus. One major pitfall in the use of intrauterine growth curves must be noted: each growth curve is only specific for its own population.[10]

Growth is determined by the inherent growth potential of the individual (genetic factors) and by nutritional and endocrine influences (environmental factors) on this genetic potential. Inherent factors affecting the genetic potential of the fetus include chromosomal aberrations and congenital malformations. Environmental factors include intrauterine infection, maternal hypoxia due to cyanotic heart disease or to constrictive pulmonary disease, severe anaemia, maternal malnutrition, alcoholism, drug addiction, smoking and reduced uteroplacental perfusion. It is only appropriate to speak of intrauterine growth retardation (IUGR) if growth is restricted by environmental factors and not by genetic factors.

Although in many cases the mechanism of intrauterine growth retardation remains unexplained, there are often indications of poor uterine or placental circulation. Theoretically, it has been estimated that growth retardation due to reduced uteroplacental circulation accounts for approximately 35% of all SGA infants born (Size at birth, 1974 pg 393). It is thus relatively common and may lead to considerable perinatal mortality and morbidity.

Data from our own department, collected from two cohorts of infants born between June 1975 and June 1978 (Groningen Perinatal Project) have shown a 4 to 5 fold increase in the risk of perinatal mortality in the group of small-for-dates infants. Furthermore there is a marked increase in neonatal neurological morbidity, when birth weights were below the 10th centile. Follow-up studies on possible neurological and mental sequelae showed few abnormalities, except in infants who were severely growth retarded or preterm as well as growth retarded.[6 7 13] These data emphasize the clinical importance of intrauterine growth retardation, especially if it occurs late in the second trimester or early in the third trimester.

Intrauterine growth retardation due to impaired uteroplacental perfusion is caused by reduced nutrient and oxygen supply to the fetus and placenta. This metabolic shortage leads to more or less progressive deterioration of the fetal condition. It must be kept in mind that the end-point of this chronic process may vary considerably, from a slightly dystrophic newborn to fetal death in utero. This also indicates that the nutritional deprivation may affect different aspects of the "fetal condition". For instance, in the case of the slightly dystrophic infant, organ function (brain, liver, kidney etc.) may only be slightly impaired, whereas in the case of impending fetal death severe hypoxaemia and acidaemia leads to profound circulatory and behavioural changes. Thus the degree to which each individual fetus may be affected differs, but the common denominator is the "reduced supply line". The question arises as to how the degree of metabolic shortage can be quantified and how its effects on each fetus can be evaluated. What markers are available? In 1983, at the start of this research project, there were no direct markers to indicate reduced supply of nutrients and oxygen to the human fetus. Umbilical cord blood sampling was possible with fetoscopy. However, due to high fetal risks this procedure has been abandoned. With the recent development of the fetal blood sampling by means of cordocentesis, some direct information on fetal metabolism has become available.[14 20] Yet, this invasive procedure is not without risk for the fetus and should only be performed on strict indications. The effects of metabolic shortage on the growth-retarded fetus have, therefore, mainly been evaluated by means of indirect markers.

Reduction in growth of the fetus is one of the first effects of chronically impaired uteroplacental circulation. Estimation of fundal height is the most common screening method for growth retardation, although the predictive value is limited. With the development of ultrasound imaging, fetal weight can be estimated with more precision and skeletal and organ growth can be measured.[11] Furthermore, asymmetrical growth, with relative sparing of brain size, can be distinguished from symmetrical growth by means of ultrasound. This leads us to brain growth and brain function, other indirect markers of reduced nutrient and oxygen supply. How can brain function in utero be evaluated? Fetal heart rate and movement patterns are indirect indicators of brain function and together with blood flow they are integrated in the cardiovascular system, which is regulated by the central nervous system. An example of this integration is the behavioural state organisation; transitions of fetal movement and heart rate patterns occur simultaneously, as well as distinct changes in blood flow velocity wave form patterns.[4]

In this thesis, the indirect markers fetal heart rate and movement patterns, will mainly be related to the circulatory and respiratory condition of the growth-retarded fetus. We are nevertheless, aware that this represents only part of the "fetal condition".

Until recently, the information as to the actual antepartum condition was restricted to fetal heart rate (FHR) monitoring and to the monitoring of fetal movements. It is known that intrauterine death is preceded by a so-called "terminal" FHR pattern, with the absence of heart rate variation ("flat" pattern) and shallow decelerations following Braxton Hicks contractions.[3 23] With such a pattern death in utero occurs within one week; at primary elective Caesarean section the majority of infants are acidaemic at birth, determined from blood taken from the umbilical cord.[23] With less severe heart rate abnormalities ("decelerative" pattern) the pH is usually still within the normal range.[8 24]

A sudden decrease in the incidence of fetal movements appears to be a reliable sign of impairment of the fetal condition; "the movement alarm signal".[15 18] In these studies data on fetal movements were obtained from subjective records kept by pregnant women. Fetal death occurred within several days after the sudden decline in fetal activity. Prior to this decline, the fetal movement incidence was within the normal range, suggesting that this reduction in fetal movements is a late sign of fetal compromise. Also in IUGR fetuses, a quantitative reduction of maternally-perceived fetal movements has been reported. However, a wide overlap appears to exist with normal fetuses.[9] Prior to the reduction in the number of maternally-perceived movements, Sadovsky et al. described an interesting phenomenon, namely a change in

the quality of the perceived movements. The number of strong movements decreased and instead the mothers felt more small and weaker movements.[19] Ultrasound data on fetal movements in intrauterine growth retardation are limited. Roberts et al. have reported a reduction in fetal trunk movements as well as fetal breathing movements in IUGR fetuses.[17] Furthermore, fetal body and breathing movements are two variables of the biophysical profile, which is a method for the antepartum evaluation of fetal well-being using real-time ultrasound.[12] Absence or a reduction of these movements lower the score of the biophysical profile score; it has been claimed that a low score identifies the compromised fetus. Data on fetal movements in relation to gaseous metabolism, as determined by blood gas analyses, are lacking.

Recently, a new non-invasive technique was developed to study the uteroplacental circulation: Doppler measurements of velocity waveforms of the umbilical artery.[16 21] It has been claimed, that these measurements provide direct and essential information on the adequacy of the placental circulation and allow early identification of those fetuses at risk of "perinatal distress".[16] Others, however, have shown that the sensitivity of umbilical artery waveforms for the detection of growth retardation, is limited.[2 25]

Statement of the problem

The present state of the art requires a number of studies on a well-defined group of growth retarded fetuses with impaired uteroplacental circulation.

1. The above-reported deterioration of the fetal condition in growth retardation affects the various organ systems, at different times and to different degrees. What is the temporal sequence of impairment of fetal heart rate, fetal movements and blood flow waveforms in the umbilical artery? Knowledge of such a sequence is of great significance for the clinician in his daily routine.
2. How is the acid-base status at delivery (elective Caesarean section) related to antepartum heart rate patterns and to fetal motility? Such a relationship might clarify the sensitivity of the aforementioned markers.
3. If the deterioration of the growth-retarded fetus is at least partly due to impaired oxygenation, the question arises as to whether transient improvement in oxygenation will also lead to transient improvement of the fetal condition; does hyperoxygenation of the fetus improve heart rate patterns and motility of the compromised fetus?

Contents

In Chapter 2, the normal fetal movement and heart rate patterns throughout gestation are discussed, as well as the development of ultradian and diurnal rhythms. The data was derived from earlier studies conducted at our department and from the literature.

In Chapter 3 a comparison is made between growth-retarded fetuses with and without antenatal late heart rate decelerations. Within 24 hours of elective Caesarean section, one-hour recordings of fetal body movements were made by real-time ultrasound, simultaneously with fetal heart rate recordings. Heart rate variation and body movements in both groups were compared and correlated with blood gases from the umbilical artery and vein.

The specific effect of isolated late heart rate decelerations (i.e. spontaneous "hypoxaemic" events) on fetal heart rate variation as well as on fetal breathing and body movements is discussed in Chapter 4.

In the next chapter (Chapter 5) a study is presented in which mothers of growth-retarded fetuses were hyperoxygenated in order to increase fetal oxygen tension and to investigate whether the effects of fetal hypoxaemia can be abolished.

In Chapter 6, the question of whether the quality and/or quantity of individual fetal movement patterns differ between fetuses with growth retardation and appropriately grown fetuses is adressed in a detailed study.

In Chapter 7 the time-relationship between abnormal Doppler velocity wave-forms of the umbilical artery and the occurrence of late heart rate decelerations is investigated. In this study an attempt was made to substantiate the earlier finding that abnormal Doppler waveforms precede heart rate decelerations, as has been suggested in the literature.[16] In Chapter 8 the findings are summarized and discussed in the light of the neonatal neurological morbidity. A possible rank order is presented in which changes in fetal behaviour, heart rate variation and umbilical artery Doppler waveform patterns occur with progressive deterioration of the fetal condition.

References

1. Battaglia FC, Lubchenco LC. (1967): A practical classification of newborn infants by weight and gestational age. J. Pediatr 71:159.

2. Beattie RB, Dornan JC. (1989): Antenatal screening for intrauterine growth retardation with umbilical artery Doppler ultrasonography. Br. Med. J. 195-199.

3. Emmen L, Huisjes, HJ, Aarnoudse JG, Visser GHA, Okken A. (1975): Antepartum diagnosis of the "terminal" fetal state by cardiotocography. Br.J Obstet. Gynaecol. 82:353.

4. Eyck J van, Wladimiroff JW, Noordam MJ, Tonge HM, Prechtl HFR. (1985): The blood flow velocity wave-form in the fetal descending aorta; its relationship to fetal behavioural states in normal pregnancy at 37-38 weeks of gestation. Early Hum. Dev. 12:137

5. Gruenwald P. (1963): Chronic fetal distress and placental insufficiency. Biol. Neonate 5:215.

6. Fitzhardinge PM, Stevens EM. (1972): The small-for-date infant. II Neurological and intellectual sequelae. Pediatrics 50:50.

7. Hadders-Algra M. (1987): Correlates of brain dysfunction in children; a follow-up study. Ph D thesis, University of Groningen

8. Henson GL, Dawes GS, Redman CWG. (1983): Antenatal fetal heart-rate variability in relation to fetal acid-base status at Caesarean section, Br. J. Obstet. Gynaecol 90:516-521

9. Jarvis GJ, MacDonald HN. (1979): Fetal movements in small-for-dates. Br. J. Obstet Gynaecol. 86:724.

10. Kloosterman GJ. (1970): On intrauterine growth. Int. J. Gynaecol. Obstet 8:141.

11. Laurin J. (1987): Intra-uterine growth retardation. Thesis, University of Lund, Malmo, Sweden.

12. Manning FA, Baskett TF, Morrison I, Lange I. (1981): Fetal biophysical profile scoring: a prospective study in 1184 high-risk patients. Am. J. Obstet. Gynecol. 140:289-294

13. Neligan GA, Kolvin I, Scott D. Mcl, Garside RF. (1976): Born too soon or born too small, a follow-up study to seven years of age. Clinics in Dev. Med. No 61. London: S.I.M.P. Heinemann Medical Books. Philadelphia: Lippencott.

14. Nicolaides KH, Soothill PW, Rodeck, CH, Campbell S. (1986): Ultrasound-guided sampling of the umbilical cord and placental blood to assess fetal well-being. Lancet i:1065.

15. Pearson JF, Weaver JB. (1976): Fetal activity and fetal well-being: an evaluation. Br. Med. J. I, 1305-1307

16. Reuwer PJHM, Sijmons EA, Rietman GW, Tiel van MWM, Bruinse HW. (1987): Intrauterine growth retardation: prediction of perinatal distress by Doppler ultrasound. Lancet ii:415-418

17. Roberts AB, Little D, Cooper D, Campbell S. (1978): Fetal activity in normal and abnormal pregnancies. Proc. 5th Fetal Breathing Conference, Nijmegen. Editor: Eskes TKAB University Press, Nijmegen. The Netherlands.

18. Sadovsky E, Yaffe H, Polishuk WZ. (1974): Fetal movement monitoring in normal and pathologic pregnancy. Int.J.Gynaecol.Obstet 12:75-79

19. Sadovsky E, Laufer N, Allen JW. (1979): The incidence of different types of fetal movements during pregnancy. Br. J. Obstet. Gynaecol. 86:10-14

20. Soothill PW, Bilardo CM, Nicolaides KH, Campbell S. (1986): Relation of fetal hypoxia to mean blood velocity in the fetal aorta. Lancet ii:1118.

21. Trudinger BJ, Giles WB, Cook CM, Bombardieri J, Collins L. (1985): Fetal umbilical artery flow velocity wave-forms and placental resistance: clinical significance. Br. J. Obstet. Gynaecol. 92:23.

22. Usher R, McClean F, Scott KE. (1966): Judgement of fetal age II: Clinical significance of gestational age and an objective method for its assessment. Pediatr. Clin. North Am. 13:835.

23. Visser GHA, Huisjes HJ.(1977): Diagnostic value of the unstressed antepartum cardiotocogram Br. J. Obstet. Gynaecol. 84:321.

24. Visser GHA, Redman CWG, Huisjes HJ, Turnbull AC. (1980): Nonstressed antepartum heart rate monitoring: implications of decelerations after spontaneous contractions. Am. J. Obstet. Gynecol. 138:429-435

25. Vugt JMG van, Ruissen KJ, Schouten HJA, Theunissen M, Hoogland HJ, Haan J de. (1988): Umbilical artery blood velocimetry: a prospective longitudinal study in search of the intrauterine growth retarded fetus. Early Hum. Dev. 18:59.

2

FETAL HEART RATE AND MOVEMENT PATTERNS IN NORMAL PREGNANCIES

Introduction

In this Chapter, fetal heart rate and movement patterns as found in uncomplicated pregnancies are briefly reviewed. Attention is paid to maturational changes, diurnal variations and to the development of fetal rest-activity cycles and behavioural states. Gaining an understanding of the normal heart rate and movement patterns throughout gestation is essential for interpreting data obtained in compromised pregnancies.

Fetal heart rate patterns

Fetal heartbeat is visible with transvaginal ultrasound from 39 days after the last menstrual period. At that gestational age (crown-rump length: 2 to 3 mm) mean heart rate is approximately 70 beats per minute. [1] Fetal heart rate increases between 6 and 10 weeks after the last menstrual period to 180 beats per minute [2], thereafter the basal rate gradually decreases to about 140 beats per minute at term.

The literature concerning neural control of heart rate is exceedingly extensive and often controversial. Discussion of the literature is beyond the scope of this thesis. From an obstetrical point of view, the literature on the regulatory mechanisms of heart rate has been summerized by Van Geijn (1980). [3] Initially the fetal heart rate pattern is completely flat. [4] Between 16 and 26 weeks of gestation large heart rate decelerations may occur and before 30 weeks decelerations are more numerous and greater than accelerations; thereafter this relationship is reversed, but decelerations following accelerations are still common in normal pregnancy near term. [5,6] The changes in heart rate probably reflect maturation of the innervation of the fetal heart. The change from decelerations to accelerations at about 30 weeks and the increase in number and size of the accelerations during the third trimester explains the fact that despite a continued fall in basal heart rate, the mean rate does not fall near term. [7]

With increasing gestational age all parameters of heart rate variation increase. Long-term variation (i.e. variation caused by accelerations and decelerations) more than doubles from 20 to 40 weeks. [5 7] This implies that during the second half of gestation, the number and size of accelerations increases. Accelerations are thought to indicate fetal well-being, if they are in excess of 15 beats per minute above the baseline. It should be noted, however, that accelerations of this size are not a consistent phenomenon in normal pregnancy before 35 weeks of gestation. [6 7] At an earlier gestational age, the use of an amplitude in excess of 10 beats per minute as a criterion for an heart rate acceleration might well increase the predictive value of this heart rate component. [9 10 11 12] Both in normal and in growth-retarded fetuses there are large interfetal differences in heart rate variation, but within the same fetus individual variation remains within a much narrower range. [7 13]

From 30 weeks onwards the lower limit of the normal range of long-term heart rate variation remains approximately the same, despite the overall increase in variation. This has been shown in studies in which heart rate variation was measured as the root-mean-square (RMS) of the deviation around the baseline [7 14] and in studies in which variation was computed as mean minute range. [15 16] This finding facilitates the identification of abnormal antenatal heart rate records. However, low heart rate variation may be a normal feature, as this has been found in some normal fetuses between 30-33 weeks of gestation. [16] Before 30 weeks the lower limit of normality has not yet been estimated precisely; it might well be lower than that of the last 10 weeks of gestation.

Besides an increase in heart rate variation and changes in the distribution of accelerations and decelerations, there is a third change in the course of pregnancy: a progressive patterning of the heart rate into episodes of low and high heart rate variation. From 27 weeks onwards, these patterns are related to the fetal rest-activity cycles. [7] In the preterm fetus the median length of a consecutive low and high variation episode is about 50 to 60 minutes. [17 18] At this age the mean length of a low variation episode is 12.5 minutes (range 6-30 minutes). [7] After 36 weeks the median length of a consectutive low and high variation episode increases to about 80 minutes, whereas the mean length of the low variation episode increases to about 20 minutes (range 6-40 minutes). [7 19 20 21] These data imply, that "non-reactive" heart rate patterns of up to 30 minutes (before 36 weeks) or 40 minutes (near term) duration, are normal findings in uncomplicated pregnancies.

Antenatal fetal heart rate decelerations are associated with fetal compromise, especially when they occur following a Braxton Hicks contraction (i.e. late decelerations) Data on the prevalence of these decelerations in uncom-

plicated pregnancies are scarce. After 30 weeks of gestation a late deceleration was found in two of 149 one-hour records made in normal pregnancies. [7] In another study, two decelerations were found in 172 one-hour records made between 37 and 39 weeks of gestation. [20] This indicates that the incidence of late heart rate decelerations in normal pregnancies is low. After excluding one deceleration, because it was associated with a prolonged contraction, these studies suggest a frequency of 1 deceleration per 107 hours. If a late deceleration in a normal pregnancy occurs by chance, the incidence of a repetitive decelerative heart rate pattern (for definition see ref. no. 22) is in the order of $(1/107)^2$ hours.

Fetal movement patterns

Spontaneous fetal movements can first be observed at 7 1/2 weeks postmenstrual age. [23] So far, analysis of fetal movements seen between 7 and 8 weeks, i.e. just discernible movements, has been impeded by the small size of the fetus and the limited resolution of the ultrasound equipment. All types of movement patterns emerging after 8 weeks are, however, specific and well recognizable. There is an early emergence of different movement patterns and at 15 weeks 15 distinct patterns can already be distinguished (startles, general movements, hiccups, breathing, isolated arm and leg movements, retroflexion/rotation and anteflexion of the head, jaw movements, sucking and swallowing, hand face contact, stretch, yawn). [23] These movements, once observed, remain present during the course of pregnancy and their appearance hardly changes. They closely resemble those observed in preterm and fullterm newborn infants, which makes it possible to classify them accordingly. [24]

During the course of normal pregnancy several quantitative changes in motility occur. These changes are related to changes in the incidence of individual movements and to the progressive clustering of fetal motility in rest-activity cycles as well as to the development of fetal behavioural states. During the first half of gestation the incidence of most movements gradually increases, some reaching a peak even before 20 weeks. The incidence of startles and hiccups, for example, declines after 12 and 13 weeks respectively, while the incidence of general movements increases rapidly until a plateau is reached at 10 weeks (about 12% of the recording time). [25]

Quantitative data on the development of movement patterns are available for the first half of gestation, but for the second half they are still incomplete and only known for general movements, breathing and hiccups.

There are no clear changes in the incidence of general movements after 20 weeks of gestation, despite the clustering that occurs. The median incidence is, in fact, identical to that from 10 to 20 weeks and varies in different studies from 10 to 16 per cent of the recording time. [14 20 26 27 28] The lower limit of this incidence does not change from 28 weeks onwards and is about 6 per cent of the recording time (in one-hour observations). [14]

The incidence of breathing movements increases until 30 weeks of gestation. The mean incidence at 20 weeks is 6 per cent and at 30 weeks 30 per cent. [25 29] Although the incidence (percentage of recording time) does not change after 30 weeks, the breathing rate gradually declines. [30] After 36 weeks regular breathing coincides with behavioural state 1F. [31] During early gestation hiccups occur every hour. Near term, only two to four bursts per 24 hours are observed [28] and recently an overall incidence of 1.2 per cent of the recording time has been reported. [32] It must be emphasized that at all ages there are large inter-individual variations in the incidence of the different types of movement, which results in wide ranges. [33]

In uncomplicated pregnacies several fetal movement patterns are closely related to heart rate changes. [32] Gaining an insight into these relationships is essential, because some heart rate patterns that might indicate fetal jeopardy ("sinusoidal" pattern) sometimes can be explained by physiological phenomena (fetal sucking). [32]

Fetal behavioural states

In the fullterm newborn infant, behavioural states are present with relatively stable periods of time with particular combinations of well-defined behavioural characteristics. At transitions between states, the different state variables change in concert. On the basis of both observational and polygraphic studies, it was concluded that in preterm infants, behavioural states emerge from about 36 weeks onwards. [34 35 36 37]

The periodicity of the different fetal movements undergo several changes during the course of gestation. For example, at 8 weeks, general movements are scattered over the record, whereas they become grouped into bursts during the following weeks. After 14 weeks, these bursts are replaced by much longer epochs of fluctuating activity. [23] Using heart rate variation (band width), body movements and eye movements as state variables, it has been demonstrated that from 30 weeks onwards the cyclic changes in these variables are significantly related. [18] Using the same state variables, Nijhuis et al [20]

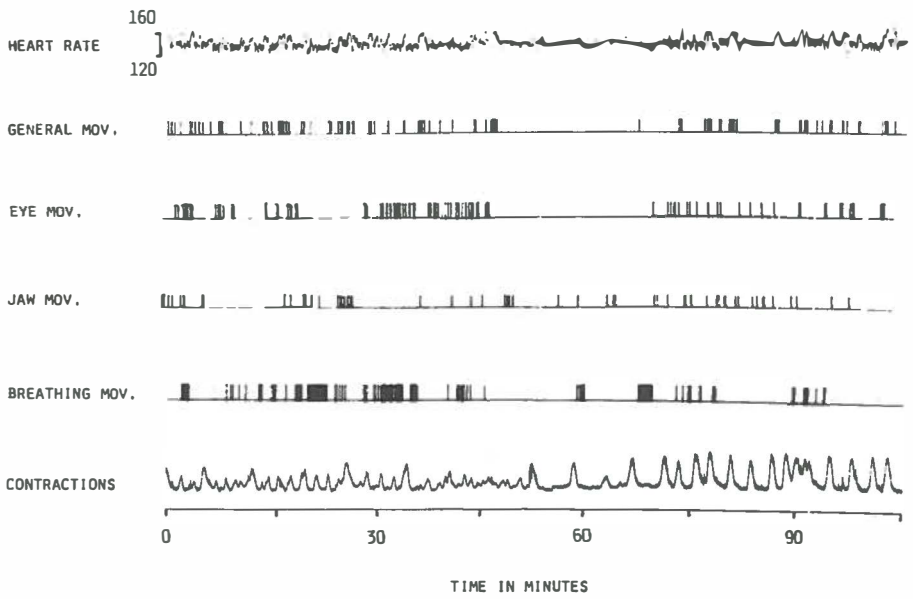

Fig. 1
Example of a coordinated heart rate and motility pattern of a 38 weeks human fetus. Two episodes of high heart rate variation with general movements and eye movements (state 2F) are interrupted by a 25 min episode of low variation; during the latter both general movements and eye movements are absent (State 1F).

showed that fully developed behavioural states are present from about 36 weeks of gestation onwards. The four distinct behavioural states, named states 1F through 4F, correspond to states 1 through 4 of the neonate, respectively. An example of a coordinated pattern of heart rate, body movements and eye movements is shown in Figure 1.

Although they are defined by other state variables, fetal behavioural states are homologous to the states described in the newborn infant. [36] Birth apparently does not constitute a major turning-point in the development of neural functions from pre-natal to post-natal life. [37] The presence of behavioural states is one of the indicators of maturity and integrity of the fetal and infant's nervous system. By studying fetal behavioural states the functional development of the nervous system can be assessed.

Diurnal variations

During the third trimester, several diurnal variations have been found in the human fetus. The incidence of gross body movements is the highest around midnight and the lowest between 09.00 and 12.00 hours. [27] Changes in the incidence of fetal heart rate accelerations occur concomitantly with the variations in these movements; the long-term heart rate variation at around midnight is about twice as high as before midday. From 21.00 hours onwards, a continuous episode with gross body movements and high heart rate variation may last for 6 hours, which implies that the rest-activity cycles, which usually have a length of about 80 minutes, are interrupted for a prolonged period of time. Fetal heart rate shows a diurnal variation of 11 per cent, which is not related to the changes in heart rate variation, with the lowest values from 02.00 to 06.00 hours and the highest between 09.00 and 12.00 hours. [20] The diurnal variations in fetal heart rate and overall motor activity are already distinguishable at 20 to 22 weeks of gestation. [38] Fetal breathing movements are related to maternal plasma glucose concentrations and significant increases are found during the second and third hour after meals. [29] Fetal breathing movements decrease over course of the day and the lowest incidence occurs between 19.00 and 24.00 hours. Fetal breathing activity increases between 04.00 and 07.00 hours: this increase is not related to maternal glucose concentrations. [20]

The origin of these diurnal variations has only partly been explained for. It is thought that maternal influences are a likely cause, because such variations are lost immediately after birth, only to recur one to two months later. [39 40] Maternal sleep is unlikely to be of importance as the changes occur before the onset of the mother's sleep. [20] On the other hand, diurnal variations in fetal heart rate follow changes in the maternal heart rate. It has recently been shown that the administration of corticosteroids (triamcinolone) can temporarily abolish the diurnal rhythm of fetal movements and heart rate variation. [41] Animal experiments have shown that fetal adrenal activity is related to maternal adrenal activity and that the former increases at night, probably because of decreased suppression from maternal adrenal activity. [42] Thus the fetal diurnal variations seem to be influenced by maternal adrenal activity. The mechanisms through which the maternal and fetal adrenal activity affect fetal movements and heart rate (variation) are still obscure.

References.

1. Schats R. (1990): PhD Thesis, University of Rotterdam, in press.

2. Robinson HP, Shaw-Dunn J. (1973): Fetal heart rates as determined by Sonar in early pregnancy. J. Obstet. Gynaecol. Br. Commonwealth, 80:805-809.

3. Geijn van HP. (1980): Studies on fetal and neonatal baseline heart rate variability. PhD Thesis, University of Nijmegen,

4. Wladimiroff JW. (1972): Tachometrie in de vroege zwangerschap; ontwikkeling van de nervus vagus functie. Nederlands Tijdschrift voor Geneeskunde, 116:1688-1693.

5. Wheeler T, Murrills A. (1978): Patterns of fetal heart rate during normal pregnancy. Br. J. Obstet. Gynaecol. 85:18-27.

6. Dawes GS, Houghton CRS, Redman CWG, Visser GHA. (1982): Patterns of normal fetal heart rate. Br. J. Obstet. Gynaecol. 89:276-284.

7. Visser GHA, Dawes GS, Redman CWG. (1981): Numerical analysis of the normal human antenatal fetal heart rate. Br. J. Obstet. Gynaecol., 88: 792-802.

8. Wheeler T, Cooke E, Murrills A. (1979): Computer analysis of fetal heart rate variation during normal pregnancy. Br. J. Obstet. Gynaecol. 86: 186-197.

9. Gagnon R, Campbell K, Hunse C, Patrick J. (1987): Patterns of human fetal heart rate accelerations from 26 weeks to term. Am. J. Obstet. Gynecol. 157:743-749.

10. Nicolaides KH, Sadovsky G, Visser GHA. (1989): Heart rate patterns in normoxemic, hypoxemic, and anemic second-trimester fetuses. Am. J. Obstet. Gynecol. 160:1034-1037.

11. Visser GHA, Sadovsky G, Nicolaides KH. (1989): Antepartum heart rate patterns in small-for-gestational age third trimester fetuses: Correlations with blood gases obtained at cordocentesis. Am. J. Obstet. Gynecol. in press.

12. Gagnon R, Hunse C, Bocking AD. (1989): Fetal heart rate patterns in small-for-gestational age human fetus. Am. J. Obstet. Gynecol. 161:779-784.

13. Snijders RM, Ribbert LSM, Franssens M, Visser GHA (1988): Heart rate variability in small-for-dates fetuses with abnormal umbilical artery velocity waveforms. Abstracts 3rd Int. Conf. on Fetal and Neonatal Measurements. (Marsal K ed.), Ronneby, Sweden, p. 87

14. Bekedam DJ, Visser GHA, Mulder EJH, Poelmann-Weesjes G. (1987): Heart rate variation and movement incidence in growth-retarded fetuses: the significance of antenatal late heart rate decelerations. Am. J. Obstet. Gynecol. 157:126-133.

15. Lawson GW, Dawes GS, Redman C. (1984): Analysis of fetal heart rate on-line at 32 weeks gestation. Br. J. Obstet. Gynaecol. 91:542-550.

16. Smith JH, Dawes GS, Redman CWG. (1987): Low human fetal heart rate variation in normal pregnancy. Br. J. Obstet. Gynaecol. 94:656-664.

17. Hoppenbrouwers T, Combs D, Ugartechea JC, Hodgman J, Sterman MB, Harper RM. (1981): Obstet. Gynecol. 57:301-309.

18. Visser GHA, Poelmann-Weesjes G, Cohen TMN, Bekedam DJ. (1987): Fetal behavior at 30 to 32 weeks of gestation. Pediatric Res. 22:655-658.

19. Junge HD. (1979): Behavioural state and state related heart rate and motor activity patterns in the newborn infant and the fetus antepartum. A comparative study. J.Perinatal Med. 7:85-107.

20. Visser GHA, Goodman JDS, Levine DH, Dawes GS. (1982): Diurnal and other cyclic variations in human fetal heart rate near term. Am. J. Obstet. Gynecol. 142:535-544.

21. Nijhuis JG, Prechtl HFR, Martin CB, Bots RSGM. (1982): Are there behavioural states in the human fetus? Early Hum. Dev. 6:177-195.

22. Visser GHA, Redman CWG, Huisjes HJ, Turnbull AC. (1980): Nonstressed antepartum heart rate monitoring: implications of decelerations after spontaneous contractions. Am. J. Obstet. Gynecol. 138:429-435.

23. De Vries JIP, Visser GHA, Prechtl HFR. (1982): The emergence of fetal behaviour. I. Qualitative aspects. Early Hum. Develop. 7:301-322.

24. Prechtl HFR, Fargel JW, Weinemann HM, Bakker HH. (1979): Posture, motility and respiration in low-risk preterm infants. Dev. Med. Child Neurol. 21:3-27.

25. De Vries JIP, Visser GHA, Prechtl HFR. (1985): The emergence of fetal behaviour. II. Quantitative aspects. Early Hum. Develop. 12:99-120.

26. Manning FA, Platt LD, Sipos L. (1979): Fetal movements in human pregnancies in the third trimester. Obstet. Gynecol. 54:699-702.

27. Roberts AB, Little D, Cooper D, Campbell S. (1979): Normal patterns of fetal activity in the third trimester. Brit. J. Obstet. Gynaecol. 86:4-9.

28. Patrick J, Campbell K, Carmichael L, Natale R, Richardson B. (1982): Patterns of gross fetal body movements over 24 hour observation intervals during the last 10 weeks of pregnancy. Am. J. Obstet. Gynecol. 142:363-371.

29. Patrick J, Campbell K, Carmichael L, Natale R, Richardson B. (1980): Patterns of human fetal breathing during the last 10 weeks of pregnancy. Obstet. Gynecol. 56:24-30.

30. Trudinger BJ, Knight PC. (1980): Fetal age and patterns of human fetal breathing movements. Am. J. Obstet. Gynecol. 137:724-728.

31. Nijhuis JG, Martin CB, Gommers S, Bouws P, Bots RSGM, Jongsma HW . (1983) The rhythmicity of fetal breathing varies with behavioural state in the human fetus. Early Hum. Dev. 9:1-7.

32. Woerden van EE. (1989) Fetal heart rate and movements: their relationship within behavioural states 1F and 2F. PhD thesis. University of Amsterdam.

33. Vries de JIP, Visser GHA, Prechtl HFR. (1988) The emergence of fetal behaviour. III. Individual differences and consistencies. Early Hum. Dev.16:85-103.

34. Dreyfus-Brisac C. (1966): Ontogénèse du sommeil chez le prématurè humain: Etude polygraphique. In: Regional Development of the Brain in Early Life (Minkowski, A. ed.) pp. 437-457. Blackwell, Oxford.

35. Parmelee AH, Wenner WH, Akiyama Y, Schultz M, Stern E. (1967): Sleep states in premature infants. Dev. Med. Child Neurol. 9:70-77.

36. Prechtl HFR. (1974): The behavioural states of the newborn infant (a review). Brain Research 76:185-212.

37. Prechtl HFR. (1984): Continuity and change in early neural development. In: Continuity of Neural Functions from Prenatal to Postnatal Life. (Prechtl HFR ed.). pp. 1-16. Blackwell Scientific Publ. Ltd., Philadelphia, PA.

38. De Vries JIP, Visser GHA, Mulder EJH, Prechtl HFR. (1987): Diurnal and other variations in fetal movement and heart rate patterns at 20-22 weeks. Early Hum. Develop. 15:333-348.

39. Hellbrügge T. (1960): The development of circadian rhythms in infants. Cold Spring Harbor Symposium on Quantitative Biology. 25:311-323.

40. Mills JN. (1975): Development of circadian rhythms in infants. Chronobiologia. 21:363-371.

41. Arduini D, Rizzo G, Parlati E, Giorlandino C, Valensise H, Dell'Acqua S, Romanini C. (1986): Modifications of ultradian and circadian rhythms of fetal heart rate after fetal-maternal adrenal gland suppression: A double blind study. Prenatal Diagnosis. 6:409-417.

42. Challis JRG, Socol M, Murata Y, Manning FA, Martin CB Jr. (1980): Diurnal variations in maternal and fetal steroids in pregnant rhesus monkeys. Endocrinology 106:1283-1288.

3

HEART RATE VARIATION AND MOVEMENT INCIDENCE IN GROWTH-RETARDED FETUSES: THE SIGNIFICANCE OF ANTENATAL LATE HEART RATE DECELERATIONS

Summary

In 37 intra uterine growth-retarded (IUGR) fetuses, combined one-hour recordings of fetal heart rate and body movements were made within 24 hours of elective Caesarean section (CS). Fetal body movements were recorded simultaneously using real-time ultrasound. The study group was divided into two subgroups, according to the presence (n=29) or absence (n=8) of antepartum late heart rate decelerations.
Correlations were made with umbilical blood gas values obtained immediately after CS. Baseline heart rate variation was reduced below the normal range in 88% of the IUGR fetuses with decelerations, but in only 37% of the group without decelerations. A reduction in fetal heart rate accelerations and body movements and an increase in mean heart rate was also only observed in the group with decelerations. Late heart rate decelerations were associated with low pO2 values in both umbilical artery and vein. It is concluded that in IUGR fetuses, reduced heart rate variation and movement incidence correlate with the presence of late heart rate decelerations antepartum and with hypoxaemia at birth.

Introduction

With progressive deterioration of the fetal condition in utero, both heart rate variation and fetal movements decrease. Just before fetal death, the baseline variability is decreased to less than 5 beats/min., with no accelerations and with late decelerations: "the terminal pattern". This condition is strongly associated with fetal acidaemia.[1]

Recently, with computerized analysis of heart rate records, an association between reduced heart rate variation and growth retardation has been established in the human fetus. In this study, late heart rate decelerations were

usually present, but acidaemia had not yet developed.[2] It was therefore concluded that the initial reduction of long-term heart rate variation is not caused by acidaemia, but by some other factor associated with growth retardation. As heart rate variation and the incidence of body movements are reduced immediately following late heart rate decelerations, it has been suggested that these reductions are associated with fetal hypoxaemia.[3]

The aim of the present study is twofold. Firstly to gain more insight as to when heart rate variation and movements decrease in the IUGR fetus. Secondly, to examine their relationship to the acid-base status at delivery. In this paper, results based on 37 IUGR fetuses are presented, with combined recordings of fetal heart rate and fetal motility obtained within 24 hours of elective Caesarean Section (CS).

Patients and Methods

The study group consisted initially of 49 patients, admitted to the obstetrical ward under the clinical diagnosis of IUGR. Excluded were infants born vaginally, infants with birth weights above the 10th percentile according to the Dutch (Kloosterman) growth curves and infants with congenital malformations. Thirty-seven fetuses, who had a weight at birth below the 10th percentile, corrected for sex, parity and gestational age, remained in the study group. While in hospital, non-stress fetal heart rate monitoring was performed daily for a minimum duration of 45 minutes. The subjects were divided into two subgroups, based on the presence or absence of late heart rate decelerations in any of the antenatal heart rate records. An example of a late heart rate deceleration is presented in Fig. 1. Fetuses with one or more late heart rate decelerations were designated as the group with decelerations (n=29). The remainder who had normal or suboptimal heart rate traces, but no detectable late heart rate decelerations, were designated as the group without decelerations (n=8). All patients were delivered by elective CS between 28 and 39 weeks of gestation. Clinical data of the patients are shown in Table 1.

The combined fetal heart rate and movement recordings discussed in this paper were all made within 24 hours of CS, 70% of which were made within 6 hours. All recordings had a duration of 60 minutes and were made with the patient in a semi-recumbent position, slightly tilted to the left. The fetal heart rate recordings were made with a Hewlett Packard cardiotocograph (8030 A). Fetal pulse intervals were derived from an abdominal electrocardiographic signal (n=15) or from a phonomagnetic signal (n=22) and were stored on a minicassette after preprocessing by a microprocessor. The data were

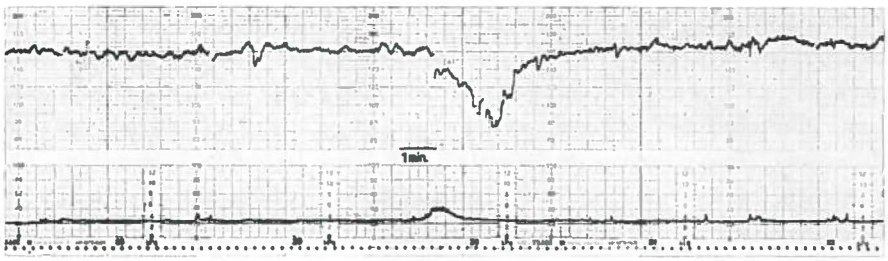

Fig. 1
An example of an antenatal late heart rate deceleration

Table 1
Clinical data of IUGR fetuses

	Group with decelerations (n=29)	Group without decelerations (n=8)
Pregnancy-induced hypertension (n)	19	4
Albuminuria (n)	13	2
Anti-hypertensive drugs (n)	5	0
Type -1- Diabetes mellitus (n)	2	0
Gestational age at birth (wk)		
Mean	33.3	35.9
Range	28-38	31-39
Birth weight (gm)		
Mean	1245	1611
Range	610-2210	950-2530
Birth weight percentile		
< 2.3	15	4
2.3-5	8	1
5-10	6	3
> 10	0	0
Stillbirth (n)	1	0
Neonatal death (n)	1	1
Intubation (n)	5	1

analysed using a previously described computer programme.[4] The baseline heart rate variation was calculated as the root mean square (RMS), after exclusion of accelerations and decelerations in excess of 40 msec (14 beats/min). Only heart rate records with a fail time of less than 70% were used in this study.[4] Three heart rate records had to be rejected for this reason. The fetal heart rate data from the growth-retarded fetuses were compared to similarly collected and processed data from 260 records made in 112 normal uncomplicated pregnancies between 28 and 40 weeks of gestation. Data on the majority of these pregnancies (n=60) have been published before.[5] In making comparisons, the effect of gestational age was taken into account.

Simultaneously with the recording of heart rate, fetal body and breathing movements were observed using a linear-array scanner (Aloka, Model SSD-256; Siemens, Imager 2300). The transducer was held in a parasagittal plane so that the fetal trunk and head were visible. Fetal body and breathing movements were recorded digitally by means of an event marker and encoded on the same tape as the fetal pulse intervals. As the fetal body movements were analysed in 3.75-second epochs, only one fetal movement was accepted every 3.75 seconds, irrespective of the frequency of pressing the button of the event marker. Data on fetal body movements from 101 one-hour records obtained in 52 normal uncomplicated pregnancies were used as controls. Pregnancy and fetal outcome in this group was uneventful. All infants were above the 10th percentile according to the Dutch (Kloosterman) curves, did well at birth and did not need special paediatric attention. These data were collected together with more recent data on heart rate variation in normal pregnancies and have been published only in part.[6 7] Data on fetal breathing movements are not included in this paper.

The patients of the study group were delivered by elective CS, because of suspected fetal distress before the onset of labour, except for one infant that died in utero. Twenty-nine women had general anaesthesia, the remaining seven were delivered under epidural analgaesia. The general anaesthesia consisted of preoxygenation with 100% oxygen at a flow rate of 10 l./min., pentothal 225-250 mg, scoline 50 mg and 0.5% halothane. The patients with epidural analgaesia were also preoxygenated as mentioned above.

At delivery the umbilical cord was double clamped and arterial and venous blood was analysed immediately for pH, pCO_2, pO_2 and base excess, using an automatic pH-blood gas analyser (RVL 940). The acid-base and blood gas values of 45 infants delivered by elective CS at 37-40 weeks of gestation were used as control values. Thirty of these infants were delivered under general anaesthesia, the remaining 15 under epidural analgaesia. Anaesthetic procedures were performed as described in the study group. All these

infants had normal antenatal heart rate records and were above the 25th percentile, according to the Dutch (Kloosterman) curves. The indications for elective termination of pregnancy before the onset of labour were breech presentation (n=16), cephalopelvic disproportion (n=25) and poor obstetrical history, but normal pregnancy (n=4). This control group was not part of the group in which the normal fetal heart rate pattern and body movement incidence were studied. Statistical significance was determined with Students t-test.

Results

In the group with decelerations, baseline fetal heart rate variation assessed numerically was below the 5th percentile of the normal range in 23 of the 26 cases (88%) (Fig. 2). In IUGR fetuses without antenatal decelerative heart rate traces, baseline heart rate variability was reduced in 3 of the 8 cases (37%) (Fig. 2). Heart rate variation in the group with decelerations was significantly reduced compared to the group without decelerations and the control group ($p<0.005$; Table 2). This reduction was also present when gestational age was taken into account.

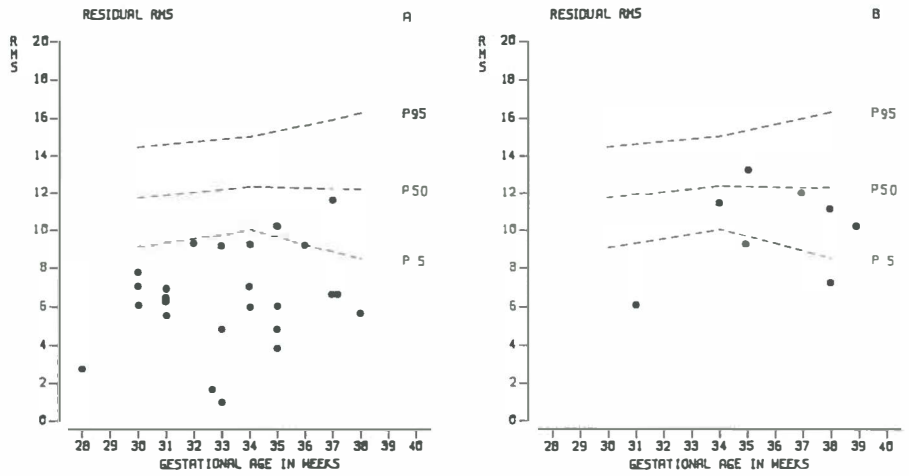

Fig. 2
Baseline heart rate variability (root mean square, RMS) of IUGR fetuses with decelerations (A) and IUGR fetuses without decelerations (B). The dotted lines indicate the percentiles of the control fetuses. Control data are based on 260 records made in 112 pregnancies.

Table 2
Baseline heart rate variation, mean heart rate, number of accelerations and gross body movements of the growth-retarded and control fetuses (mean ± SEM; number of records in brackets)

Gestational Age (wks)	IUGR group			Control group
	With decelerations	Without decelerations	Combined	
Baseline Heart Rate Variation (RMS in msec.)				
28-32	6.7 ± 0.6 (10)	6.9 (1)	6.7 ± 0.5 (11)	11.9 ± 0.2 (48)
33-36	6.5 ± 0.9 (11)	11.3 ± 1.1 (3)	7.6 ± 1.1 (14)	12.3 ± 0.2 (80)
37-40	7.0 ± 1.2 (5)	10.2 ± 1.0 (4)	8.4 ± 0.9 (9)	12.3 ± 0.2 (132)
Combined 28-40	6.9 ± 0.5 (26)	10.2 ± 0.8 (8)	7.5 ± 0.5 (34)	12.3 ± 0.2 (260)
Mean Heart Rate (Beats/min)				
28-32	148.1 ± 2.9 (10)	157.7 (1)	149.0 ± 3.3 (11)	141.5 ± 0.9 (48)
33-36	147.1 ± 3.0 (11)	140.5 ± 3.3 (3)	145.7 ± 2.5 (14)	141.0 ± 0.8 (80)
37-40	146.4 ± 1.2 (5)	136.3 ± 4.1 (4)	141.9 ± 2.5 (9)	141.0 ± 0.8 (132)
Combined 28-40	147.4 ± 1.7 (26)	140.6 ± 3.4 (8)	145.8 ± 1.6 (34)	141.1 ± 0.5 (260)
No. of Accelerations (>40 msec. and >15 sec.) per hour				
28-32	0.1 ± 0.1 (10)	0.0 (1)	0.1 ± 0.1 (11)	4.4 ± 0.8 (48)
33-36	0.4 ± 0.4 (11)	7.3 ± 5.0 (3)	1.9 ± 1.2 (14)	11.8 ± 0.9 (80)
37-40	0.8 ± 0.6 (5)	10.5 ± 4.3 (4)	5.1 ± 2.5 (9)	14.4 ± 0.7 (132)
Combined 28-40	0.4 ± 0.2 (26)	8.0 ± 2.9 (8)	2.2 ± 0.9 (34)	11.7 ± 0.5 (260)
Gross Body Movements (% of time)				
28-32	4.6 ± 0.9 (12)	6.9 (1)	4.8 ± 0.8 (13)	14.5 ± 0.8 (26)
33-36	7.6 ± 1.9 (12)	12.9 ± 3.5 (3)	8.7 ± 2.2 (15)	12.6 ± 0.9 (26)
37-40	4.4 ± 0.6 (5)	16.1 ± 6.8 (4)	9.6 ± 3.5 (9)	17.6 ± 1.2 (49)
Combined 28-40	5.8 ± 0.9 (29)	13.7 ± 3.6 (8)	7.5 ± 1.2 (37)	15.7 ± 0.8 (101)

The mean heart rate was significantly increased in the group with decelerations compared to controls, although usually it was still within the normal range ($p<0.005$; Table 2). The mean heart rate in the IUGR fetuses of the group without decelerations was not significantly different from that in the control group.

The number of accelerations per hour exceeding 40 msec (≈14 beats/min) and lasting more than 15 sec were significantly reduced in the group with decelerations ($p<0.005$; Table 2). The group without decelerations had accelerations within the normal range (Table 2). This was in accordance with the fetal movement incidence in both groups. The lower limit (5th percentile) of normal fetal activity was rather constant throughout the last trimester (Fig. 3). A reduction in movement incidence below the 5th percentile of the normal group occurred in 69% of the fetuses in the group with decelerations, whereas fetal movements were slightly reduced in only two of the eight cases (25%) in the group without decelerations (Fig. 3). The movement incidence in the combined growth retarded group was significantly lower than in the control fetuses ($p<0.005$; Table 2). As indicated, this was due to the reduction in movement incidence in the group with decelerations (Table 2).

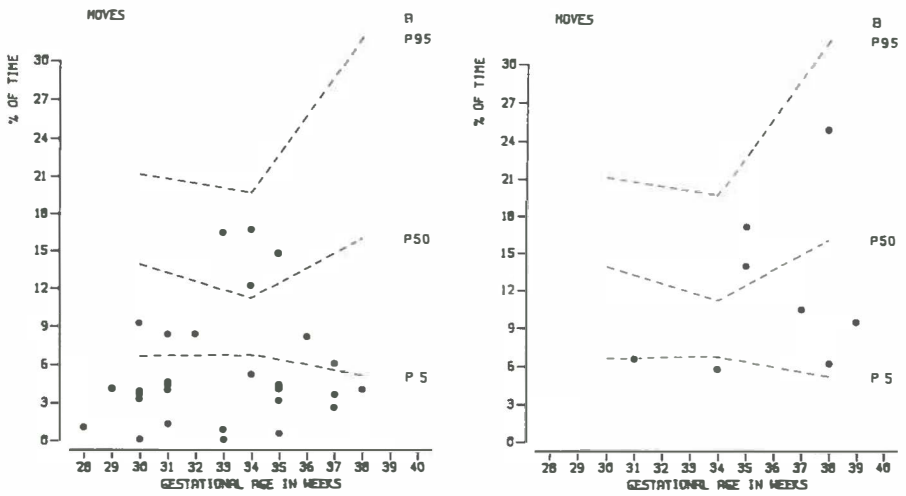

Fig. 3
Fetal body movements (% of time) of IUGR fetuses with decelerations (A) and IUGR fetuses without decelerations (B). The dotted lines indicate the percentiles of the control fetuses. Control data are based on 101 records made in 52 pregnancies.

In Figs 4 and 5, pH and pO_2 values in the umbilical artery and vein are shown. In most of the 36 IUGR fetuses (72%) umbilical artery pH was above 7.20. The mean arterial and venous pH values in the group with decelerations were lower than those in the control group ($p<0.05$) even though most values were within the normal range (Fig. 4). In contrast, pO_2 values in both umbilical artery and vein were remarkably low in the group with decelerations (Fig. 5). Differences between this group and the group without decelerations and the control group were highly significant ($p<0.005$). No significant differences were found in pCO_2 and base excess values between either the growth retarded group or the control group. Table 3 summarizes all the blood gas values. To exclude possible effects of pH changes on oxygen tension, pO_2 umbilical artery values in IUGR fetuses with a umbilical artery pH between 7.20 and 7.28 were compared to those in control group fetuses, whose umbilical artery pH was in the same range. Again a significant difference in pO_2 was found $p<0.005$; Table 4).

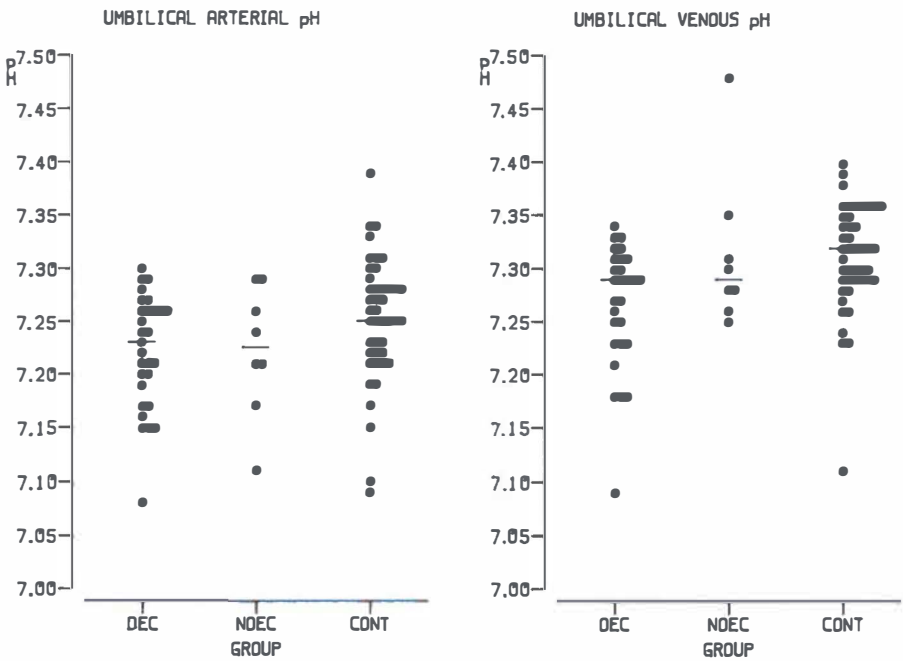

Fig. 4
Umbilical artery and vein pH values of IUGR with decelerations, IUGR without decelerations and control fetuses.

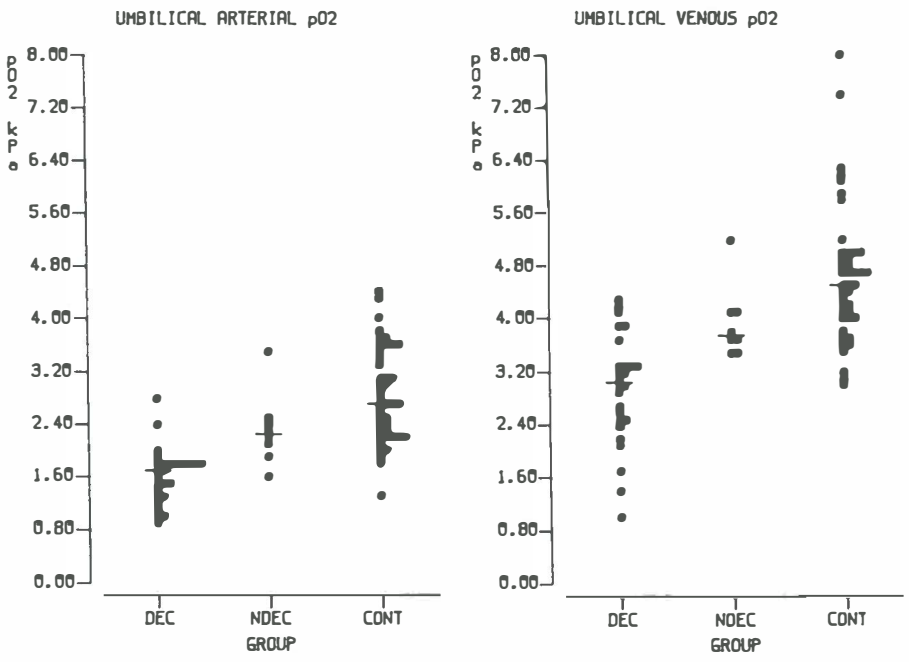

Fig. 5
Umbilical artery and vein pO_2 values of IUGR with decelerations, IUGR without decelerations and control fetuses (kPa).

To analyse the association between reduced baseline heart rate variation and low oxygen tension, IUGR fetuses with low and high heart rate variation were compared. A cut-off point was chosen at a baseline variation of 8 msec., as this was approximately 2SD below the mean baseline heart rate variation. IUGR fetuses with a variation of less than 8 msec. (n=21) had significantly lower arterial and venous pO_2 values than those with a variation of greater than 8 msec. (n=12) ($p<0.05$). The group with a very low baseline heart rate variation included 19 (76%) of the IUGR fetuses with late heart rate decelerations. Only two (25%) of the IUGR fetuses without decelerations had a baseline heart rate variation of below 8 msec. No differences existed in umbilical artery and vein pH and base excess. In the group with the lowest heart rate variation, pCO_2 values were significantly higher ($p<0.05$; Table 5).

Table 3
Blood gas values (mean ± SD) of IUGR fetuses and control fetuses at elective Caesarean section.

	IUGR group		
	With decelerations (n=28)	Without decelerations (n= 8)	Control group (n=45)
pH			
Umbilical artery	7.22 ± 0.05*	7.22 ± 0.06	7.25 ± 0.06
Umbilical vein	7.27 ± 0.06*	7.31 ± 0.07	7.31 ± 0.05
pO_2 (kPa)			
Umbilical artery	1.61 ± 0.42†#	2.29 ± 0.55	2.81 ± 0.76
Umbilical vein	2.95 ± 0.83†#	3.96 ± 0.56	4.66 ± 1.09
pCO_2 (kPa)			
Umbilical artery	7.68 ± 1.27	7.08 ± 0.83	7.30 ± 1.30
Umbilical vein	6.66 ± 1.27	5.89 ± 0.31	5.92 ± 0.90
Base Excess			
Umbilical artery	-6.42 ± 3.45	-7.00 ± 3.05	-4.89 ± 3.38
Umbilical vein	-5.74 ± 3.01	-5.73 ± 2.22	-4.01 ± 2.01

*Group with decelerations vs. Control group $p<0.05$.
†Group with decelerations vs. Group without decelerations $p<0.005$.
#Group with decelerations vs. Control group $p<0.005$.

Table 4
Comparison of pO_2 values of IUGR fetuses with decelerations and controls with umbilical artery pH values in the same range (mean ± S.D.).

	IUGR Group with decelerations (n=17) 7.20 < umbilical artery pH < 7.28	Control Group (n=25) 7.20 < umbilical artery pH < 7.28
pO_2		
Umbilical artery	1.55 ± 0.38	2.69 ± 0.64*
Umbilical vein	3.27 ± 0.56	4.21 ± 0.90*

*p<0.005

Table 5
Comparison of blood gas values of IUGR fetuses with lower and higher heart rate variation; cut-off point Root mean square of 8 msec. (mean ± S.D.)

	Root mean square < 8 (n=21)	Root mean square > 8 (n=12)
pH		
Umbilical artery	7.23 ± 0.04	7.23 ± 0.06
Umbilical vein	7.28 ± 0.04	7.31 ± 0.06
pO_2		
Umbilical artery	1.65 ± 0.49	2.11 ± 0.60*
Umbilical vein	3.24 ± 0.64	3.81 ± 0.61*
pCO_2		
Umbilical artery	7.91 ± 0.83	7.03 ± 0.92*
Umbilical vein	6.57 ± 0.73	5.87 ± 0.56*
Base Excess		
Umbilical artery	-5.48 ± 3.08	-6.96 ± 3.44
Umbilical vein	-5.04 ± 2.55	-6.84 ± 4.31

*p<0.05

Discussion

This study confirms earlier findings [2 8], that in growth-retarded fetuses long-term heart rate variation (i.e. baseline variation and variation caused by accelerations and decelerations) is usually low. Yet, in the absence of late heart rate decelerations, baseline variation is nearly always within the normal range.[8] In the presence of late decelerations, however, baseline variation and the incidence of accelerations are reduced. These data imply that before late decelerations appear, the heart rate variation pattern of the growth-retarded fetus cannot be distinguished from that of the non-compromised fetus. Consequently, reduction of long-term variation has to be considered a rather late sign of fetal compromise. At this stage of deterioration, fetal acidaemia has not yet developed, as 80% of the fetuses with reduced variation had an umbilical artery pH equal or above 7.20. This confirms the findings of Henson et al. that the initial reduction of heart rate variation is not caused by acidaemia.[2] However, remarkably low pO_2 values in both umbilical artery and vein were found in the IUGR fetuses with decelerations. In this group, hypoxaemia was consistently present at elective CS, in contrast to IUGR fetuses without decelerations whose pO_2 values were within the normal range. As the lowest pO_2 values were found in fetuses with a reduced heart rate variation, it is tempting to assume an association between chronic fetal hypoxaemia and the reduction of heart rate variation. Just before fetal death, heart rate variation is usually extremely low and decelerations are mostly shallow in character and follow each Braxton Hicks' contraction. Acidaemia is present in 70% of the cases with this "terminal" pattern at CS.[1] These late decelerations differ from those found in growth-retarded fetuses in whom only hypoxaemia is present. With the "terminal" pattern, variation is low during the deceleration, whereas in the group with decelerations an increase in variation was often found (Fig. 1). It might well be that the aetiological backgrounds of these two types of decelerations are different. Court and Parer[9] have described two possible mechanisms. The first mechanism is increased vagal activity due to chemoreceptor activation without reduced myocardial oxygen consumption. The increased heart rate variation often seen during these decelerations may be caused by simultaneously increased ß-adrenergic activity. The second mechanism occurs in terminal patterns, where hypoxic myocardial depression predominates increased vagal activity. In these cases, heart rate variation during the deceleration is reduced.

The present findings agree with those of Murata et al.,[10] who found that in rhesus monkeys with progressive deterioration in fetal condition, late decelerations appeared first. This condition, which was associated with fetal hy-

poxaemia, was followed by a decrease in accelerations (and of movements?) and a gradual decline in the pH. Reduced pO_2 values found in carunculized fetal sheep also confirmed the relationship between growth retardation and chronic hypoxaemia.[11] The fetus can tolerate moderate hypoxia, in part by a reduction in oxygen consumption.[12] On the other hand, raised haematocrit and increased oxygen extraction[12] are other compensatory mechanisms, which occur when oxygen delivery decreases. The mechanisms and pathways underlying a reduction in heart rate variation still remain obscure. Suppression of the activity of medullary centres by endogenous opiates, such as ß-endorphin, is one of the possibilities to which attention has been drawn recently.[13]

Estimating the respiratory status of the fetus in utero by means of the acid-base status at CS has to be done very cautiously. The effects of anaesthesia and surgical intervention must not be underestimated. Yet the differences in pO_2 found in this study were so profound that we predict that they will be confirmed if precise assessment of the antenatal respiratory status in the human is performed. With the rapid development of the umbilical cord blood sampling technique, under ultrasound guidance, this will be possible in the very near future.

The increased mean heart rate in IUGR fetuses with late decelerations has, to our knowledge, not been described before. As the number of accelerations is reduced, it must be concluded that the increase in mean heart rate is due to an increase in baseline heart rate. Intrapartum tachycardia is, however, a well-known phenomenon of fetal compromise and Dalton et al. have reported higher basal fetal heart rates in hypertensive pregnancies.[14] In the control fetuses, mean heart rate did not decrease during the third trimester (Tabel 2). This has been shown before and can be explained by an increase in heart rate accelerations (number and size) with gestational age, with a simultaneous fall in basal heart rate.[5] In growth-retarded fetal sheep, mean heart rates in the basal condition were also reported to be higher, than those of control animals, probably due to the increased levels of cathecholamines.[15] These findings suggest that the fetus adapts to chronic compromise by making changes in the cardiovascular system. One mechanism of adaptation is that of an increase in the basal heart rate.

In control fetuses, the mean percentage of time fetal movements were present was consistent throughout the last trimester. No decline in mean activity was noted at the end of pregnancy. The normal range of fetal activity was wide, with a marked increase in range after 36 weeks of gestation, probably due to the development of behavioural states.[16] The 5th percentile of movement incidence was, however, rather stable. Therefore a well-chosen

cut-off point in the normal fetal movement incidence might be of clinical value in the detection of the fetus at risk. In most IUGR fetuses without late heart rate decelerations, movement incidence was within the normal range. In IUGR fetuses with decelerations, the quantity of motor output was reduced. However, approximately 30% of these fetuses had a movement incidence within the normal range. This implies that while a marked reduction of movements is a sinister sign, a quantitatively normal motor output does not guarantee fetal well-being. The reduction of fetal movements in growth retardation has also been reported by other investigators, mostly using non-imaging methods.[17] Chronic hypoxaemia might account for this reduction in fetal activity. The intermittent occurrence of acute hypoxaemia is another possibility, because it has been reported that superimposed acute hypoxaemic events, as indicated by late heart rate decelerations, abolish or reduce fetal body movements in the human fetus.[3] In fetal sheep acute experimental hypoxia also reduces fetal trunk and limb movements.[18 19]

From the present study it can be concluded that in IUGR fetuses reductions in heart rate variation and motility occur before the development of acidaemia and that these changes are associated with late heart rate decelerations and fetal hypoxaemia. In general a growth-retarded fetus will be found to have normal heart rate and motility pattern. It is not growth retardation that is detected by these assessment techniques, but presumably the effects of chronic fetal hypoxaemia.

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References

1. Visser GHA, Redman CWG, Huisjes HJ and Turnbull AC. (1980): Nonstressed antepartum heart rate monitoring: Implications of decelerations after spontaneous contractions. Am.J.Obstet.Gynecol. 138:429.

2. Henson GL, Dawes GS and Redman CWG. (1983): Antenatal fetal heart rate variability in relation to fetal acid-base status at caesarean section. Br.J. Obstet.Gynaecol. 90:516.

3. Bekedam DJ and Visser GHA. (1985): Effects of "hypoxemic events" on breathing, body movements and heart rate variation. A study in growth retarded human fetuses. Am.J.Obstet.Gynecol. 153:52.

4. Dawes GS, Visser GHA, Goodman JDS, and Redman CWG. (1981): Numerical analysis of the human fetal heart rate: The quality of ultrasound records. Am.J.Obstet.Gynecol. 141:43.

5. Visser GHA, Dawes GS and Redman WG. (1981): Numerical analysis of the normal human antenatal fetal heart rate. Br.J.Obstet.Gynaecol. 88:792.

6. Visser GHA, Zeelenberg HJ, De Vries JIP and Dawes GS. (1983): External physical stimulation of the human fetus during episodes of low heart rate variation. Am.J.Obstet.Gynecol. 145:579.

7. Mulder EJH and Visser GHA. (1987): Braxton Hicks and motor behavior in the near term human fetus. Am.J.Obstet.Gynecol. 156:543.

8. Visser GHA. (1984): Antenatal cardiotocography in the evaluation of fetal well-being. Aust.NZ.J.Obstet.Gynaecol. 24:80.

9. Court DJ and Parer JT. (1984): Experimental studies of fetal asphyxia and fetal heart rate interpretation. In: Research in Perinatal Medicine. Eds. Nathanielsz, P.W. and Parer, J.T.Perinatology Press, p.113.

10. Murata Y, Martin CB, Ikenone T, Hashimoto T, Taira S, Sagawa T, and Sakata H (1982): Fetal heart rate accelerations and late decelerations during the course of intra-uterine death in chronically catheterized rhesus monkeys. Am.J.Obstet.Gynecol. 144:218-223.

11. Robinson JS, Kingston EJ, Jones CT and Thorburn GD. (1979): Studies on experimental growth retardation in sheep. The effect of the removal of endometrial caruncles on fetal size and metabolism. J.Dev.Physiol. 1:45.

12. Owens J.A., Alotta E, Falconer J and Robinson JS. (1985): Effect of restricted placental growth upon oxygen and glucose delivery to the fetus. In: The Physiological Development of the Fetus and Newborn. Eds. Jones, C.T. and Nathanielsz, P.W. Academic Press, London, p. 33.

13. Hofmeyr GJ, Bamford OS, Dawes GS and Parkes MJ. (1985): High frequency heart rate variability in the fetal lamb. In: The Physiological Development of the Fetus and Newborn. Eds. Jones, C.T. and Nathanielsz, P.W. Academic Press, London, p. 439.

14. Dalton KJ, Dawson AJ and Newcombe RG. (1985): Fetal heart rate changes in hypertensive pregnancies. In: The Physiological Development of the Fetus and Newborn. Eds. Jones C.T. and Nathanielsz P.W. Academic Press, London, p. 753.

15. Robinson JS, Jones CT and Kingston EJ. (1983): Studies on experimental growth retardation in sheep. The effects of maternal hypoxemia. J.Dev.Physiol. 5:89.

16. Nijhuis JG, Prechtl HFR, Martin CB and Bots RSGM. (1982): Are there behavioural states in the human fetus? Early Hum.Dev. 6:177.

17. Jarvis GJ and MacDonald HN. (1979): Fetal movements in small-for-dates babies. Br.J.Obstet.Gynaecol. 86:724.

18. Natale R, Clewlow F and Dawes GS. (1981): Measurement of fetal forelimb movements in the lamb in utero. Am.J.Obstet.Gynecol. 140:545.

19. Martin Jr, CB Voermans TMG and Jongsma HW. (1985): Effect of hypoxia on trunk movements in fetal sheep. 32nd Meeting Society for Gynaecol.Invest. Phoenix, Arizona, p.169.

4

Effects of "hypoxaemic" events on breathing, body movements and heart rate variation: a study in growth-retarded human fetuses

Summary

In 14 growth-retarded human fetuses, breathing and body movements were studied before, during and after late heart rate decelerations. Heart rate variation was measured before and after the decelerations. Breathing and body movements were significantly reduced during and after the deceleration. Heart rate variation was reduced after the decelerative episode. As late heart rate decelerations are presumably signs of acute fetal hypoxaemia there is evidence that these reductions are caused by hypoxaemia. The results furthermore suggest that, just as in fetal sheep, these changes might be mediated by a change in brain activity state.

Introduction

In compromised growth retarded human fetuses, heart rate variation and breathing and body movement incidence are often reduced.[1 2 3] Reduction in heart rate variation and a fall in body movement incidence below the normal range, usually take place at about the same time as the occurrence of late heart rate decelerations.[4 5] This strongly suggests that hypoxaemia may be associated with these reductions. In animal experiments it has indeed been shown that acute fetal hypoxaemia causes a cessation or reduction of fetal breathing and limb movements.[6 7] Although in the human fetus hypoxaemia has been induced, such experiments are beyond bounds for ethical reasons.[8] Spontaneous late heart rate decelerations on the other hand simulate experimental hypoxaemic conditions, as it has been shown that decelerations are associated with acute fetal hypoxaemia.[9 10] To investigate the effect of acute hypoxaemic events in the human growth-retarded fetus we compared heart rate variation and breathing and body movement incidence before,during, and after late heart rate decelerations.

Patients and Methods

This investigation was part of a study on fetal heart rate (FHR) and movement patterns in growth-retarded fetuses. To date, 82 combined one hour records of FHR and movements have been made in 24 women who eventually gave birth to a growth-retarded infant (birth weight less than the 10th percentile corrected for sex, parity and gestational age, according to the Dutch (Kloosterman) curves). In 24 of these records, made in 14 women, an isolated late heart rate deceleration was identified; the criterion for an isolated deceleration was, that no other late deceleration was recorded within 15 minutes before or after the studied one. In 22 of the 24 cases the decelerations were preceded by externally recorded Braxton Hicks contractions. On two occasions, no contraction was observed; the shape of the deceleration was, however, identical to that of the decelerations that occurred following a contraction. Clinical data on the 14 patients and the outcome are shown in Table 1. There were no stillbirths and all infants survived.

Records were made with the patients lying in a semi-recumbent position, slightly tilted to the left. FHR records were obtained with a Hewlett Packard cardiotocograph (8030A). Fetal pulse intervals were derived from an abdominal electrocardiographic signal or from a phonomagnetic signal and were

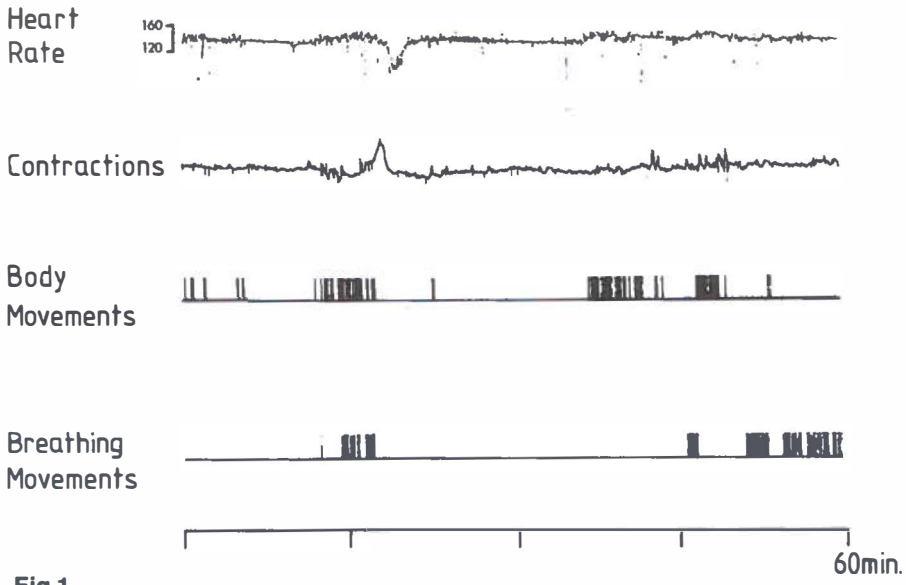

Fig.1
Example of a one-hour record (gestational age 32 weeks).

stored on a minicassette following preprocessing using a microprocessor.The data were analysed using a computer programme of which a detailed description has been published in the past.[11] The basal heart rate was calculated using an autoregressive digital filter. Variations around the basal heart rate (accelerations and decelerations)were calculated as the RMS value (root mean square of the deviation around the mean value). These values were derived for each of the 60 consecutive one-minute epochs.

Fetal breathing and body movements were observed using a linear array real time scanner (Searle or Aloka 256SD). The transducer was held in a parasagittal plane, so that the fetal chest and head were visible. Fetal body and breathing movements were recorded digitally by means of an event marker and encoded onto the same tape as the fetal pulse intervals. Data were subsequently analysed in 3.75 sec epochs. Only one fetal body movement was scored per 3.75 sec epoch, irrespective of the frequency of pressing the button. Breathing was recorded up to a peak frequency of 144 breaths/min. The data were also recorded on a 4-channel recorder (Hewlett-Packard,7754A). An example of a one-hour record is presented in Fig. 1.

Table 1
Clinical data of the study group (n=14)

Pregnancy induced hypertension (n)	10
Proteinuria (n)	5
Antihypertensive drugs (n)	3
Mode of delivery (n)	
Caesarean section	13
vaginal	1
Gestational age (wk)	
Mean	33.1
Range	29-38
Birth weight (gm)	
Mean	1200
Range	620-2210
Apgar score	
1 min	
Mean	5.6
SD	2.73
3 min	
Mean	8.1
SD	1.9
pH, umbilical artery (n=13)	
Mean	7.21
SD	0.045

Body and breathing movements were counted during the late deceleration and in the 15 minutes before and after it. Their incidence during the deceleration was normalized by conversion to rate per 5 minutes. As long term heart rate variation always increases during a deceleration, variation was only studied in the episodes before and after the deceleration.

Changes in heart rate variation, movements and breathing incidence following late decelerations may be caused by "hypoxaemia", but also by the preceeding Braxton Hicks contractions. Therefore in the same group of patients similar measurements were also made on 22 Braxton Hicks contractions that were not followed by heart rate decelerations.

Results

The mean duration of the decelerative period was 3.04 minutes (range 2-9 min.). The mean heart rate did not differ significantly in the 15 minutes before and after the decelerative period (146.5 vs 147.4). Heart rate variation increased in the 15 minute period preceding the deceleration (Fig. 2a). The variation was significantly lower during the first 5 minutes after the deceleration than during the corresponding preceding period ($p<0.05$, Wilcoxon Signed Rank Test).

In 16 of the 24 observations, breathing movements were present in the 15 minute episode before the onset of the deceleration. In all 16 these movements ceased or were significantly reduced both during the deceleration and the first 5 minutes afterwards ($p<0.01$ Wilcoxon Signed Rank Test, Fig. 3a). Seven of the 8 fetuses not breathing prior to the deceleration showed no breathing activity afterwards either.

Fetal body movements were present before the onset of the deceleration in 20 of the 24 observations. In general, a deceleration was preceded by an increase of movements (Fig 4a). Reduction or cessation occurred in all fetuses during the deceleration ($p<0.01$, Wilcoxon Signed Rank Test). During the first 5 minutes following the deceleration, movements were arrested or reduced in 15 of the 20 fetuses ($p<0.05$, Wilcoxon Signed Rank Test, Fig. 4a) .The mean percentage of time spent moving in the last 10 minutes before the deceleration was 8.1 ± 1.3% (SEM). This percentage was significantly higher than during and after the deceleration (0.8% and 5.6% respectively, $p<0.005$, Student's t Test). The four fetuses with no movements before the deceleration, didn't move during or afterwards either.

No significant difference in FHR variation, number of breaths, or incidence of body movements was found before, during and after Braxton Hicks contractions not associated with late heart rate decelerations (Figs 2b, 3b, 4b).

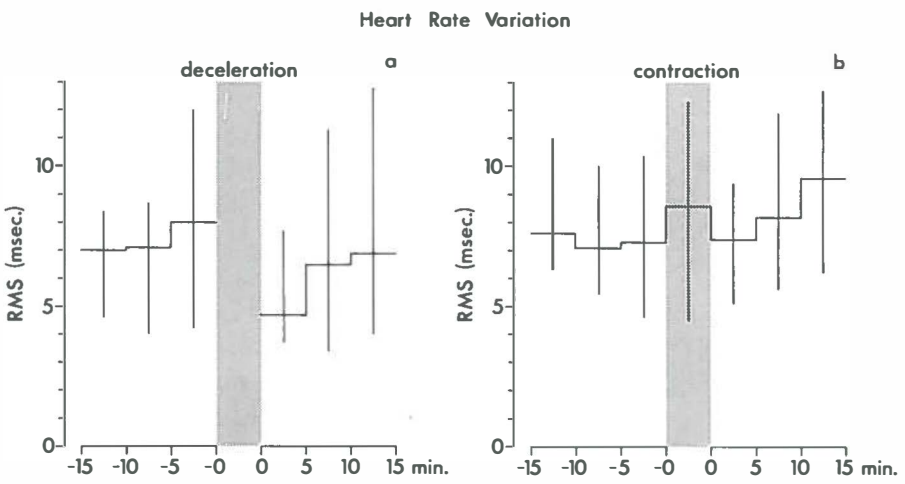

Fig. 2
Heart rate variation before and after late heart rate decelerations (a) and before,during and after Braxton Hicks contractions not associated with heart rate decelerations (b) (median RMS values and interquartile ranges).

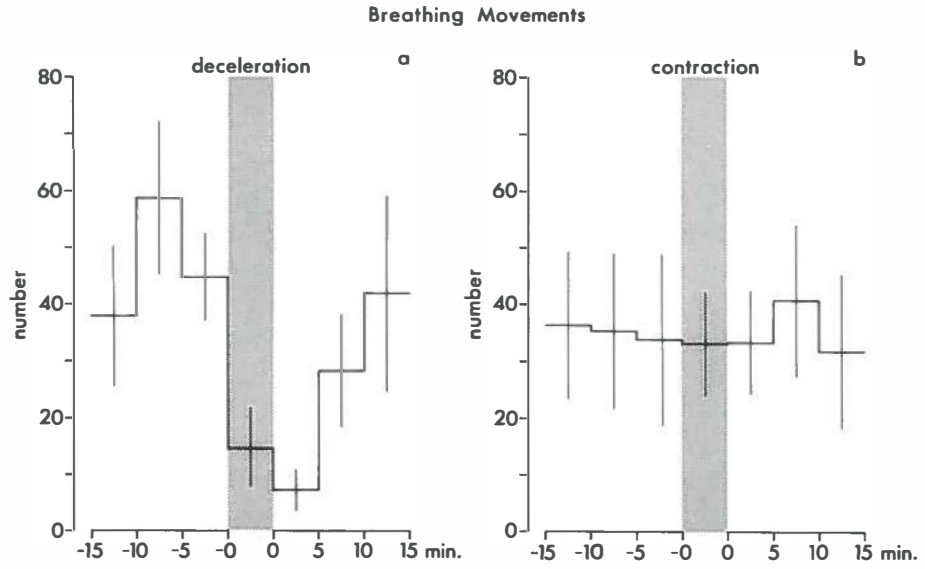

Fig. 3
Number of breathing movements per 5 minutes before, during and after late heart rate decelerations (a) and before, during and after Braxton Hicks contractions not associated with heart rate decelerations (b) (mean and SEM).

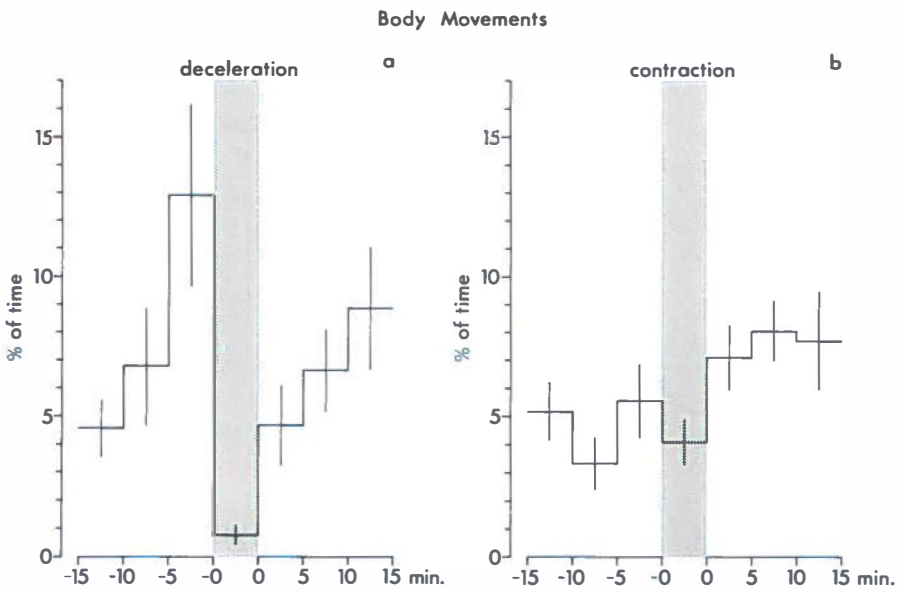

Fig. 4
Body movements, before, during and after late heart rate decelerations (a) and before, during and after Braxton Hicks contractions not associated with heart rate decelerations (b) (mean and SEM).

Comment

These data show that in growth-retarded human fetuses, breathing and body movements are reduced during and directly following late FHR decelerations. Long-term heart rate variation is also reduced after these decelerations. As late decelerations are presumably signs of acute hypoxaemia[9 10], the results strongly suggest that these reductions are caused by hypoxaemia, especially since Braxton Hicks contractions without FHR decelerations did not influence these variables.

In growth-retarded fetuses long-term heart rate variation and body movement incidence usually fall below the normal range at about the same time as the occurrence of late heart rate decelerations.[4 5] In part, this can be explained by the reduction during and following the acute hypoxemic events (late decelerations). However, chronic hypoxaemia, which probably underlies the occurrence of the decelerations, may also play a role.

The data regarding fetal breathing agree with studies on induced hy-

poxaemia in fetal sheep.[6 12] In human fetuses, only Boddy and Dawes[13] have reported a reduction of fetal breathing associated with hypoxaemia. However, their results were not suitable for statistical analysis, and the A-scan technique applied at that time had several limitations. Dornan and Ritchie[14] found that maternal hyperoxia increases the incidence of breathing in growth-retarded fetuses, but not in normal fetuses, suggesting, that hypoxaemia plays a role in the reduction of breathing. In the absence of late heart rate decelerations, we observed no difference in breathing movements before, during and after Braxton Hicks contractions (Fig. 3b). This is in agreement with the findings of Wilkinson and Robinson[15] in uncomplicated pregnancies, although these authors did observe a decrease in incidence before the peak of the contraction, with an increase directly afterwards. They related the observed changes to pressure on the fetus during the contraction and thought they were probably unrelated to changes in fetal oxygenation.

On three occasions we observed extremely large breathing movements during the nadir of the deceleration. Similar observations have been made by Boddy and Dawes[13] in the human fetus and by Harding et al.[12] in fetal sheep. We observed that these movements coincided with mouth movements. This suggests the possibility, that these might be gasping movements. However, the movement pattern was not identical to postnatal gasping, because no retroflexion of the head was observed. In fetal sheep it was suggested that these inspiratory movements were an expression of arousal, caused by the acute hypoxaemic event.[12]

The reduction and/or abolition of fetal body movements during late heart rate decelerations conforms with studies on induced hypoxaemia in fetal sheep.[7] Although body movements usually reappear soon after the deceleration, the overall incidence is transiently reduced. The same holds for long term FHR variation. Either a direct effect of reduced oxygenation or a change in brain activity state might be responsible for these reductions. In three observations in which fetal eye movements were also recorded, a cessation of these movements was observed during and after the deceleration. According to Nijhuis et al.[16] eye movements, gross body movements and heart rate variation are fetal behavioural state criteria. The concomittant change of these variables following hypoxaemia suggests a change in fetal brain activity state. Observations in humans of changes in fetal behavioural states after prolonged uterine contractions associated with heart rate decelerations also fit into this picture[17], as do observations of the effects of induced hypoxaemia in fetal sheep.[12 18]

Prior to the deceleration, an increase in the number of fetal body movements and in heart rate variation was often noted. This increase was not seen

prior to Braxton Hicks contractions without late decelerations. Fetal hypoxaemia may on one hand be caused by a reduction in oxygen supply (uterine contractions) and on the other hand by an increase in oxygen consumption (fetal movements). It may therefore well be that in growth-retarded fetuses, late heart rate decelerations occur, particularly when both a contraction and movements are present, thus causing a fall in pO_2 below a "critical" level.

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References

1. Jarvis GJ and MacDonald HN. (1979): Fetal movements in small-for-dates babies. Br. J. of Obstet.Gynaecol. 86:724.

2. Trudinger BJ, Lewis PJ and Pettit B. (1979):Fetal breathing patterns in intrauterine growth retardation. Br.J. Obstet. Gynaecol. 86:432.

3. Henson GL, Dawes GS and Redman CWG. (1983): Antenatal fetal heart rate variability in relation to fetal acid-base status at caesarean section. Br. J. Obstet. Gynaecol. 90:516.

4. Visser GHA. (1984): Antenatal cardiotocography in the evaluation of fetal well-being. Aust NZ J. Obstet. Gynaecol. 24:80.

5. Bekedam DJ, Visser GHA, Mulder EJH and Poelmann-Weesjes G. (1987): Heart rate variation and movement incidence in growth retarded fetuses: The significance of antenatal late heart rate decelerations. Am. J. Obstet. Gynecol. 157:126.

6. Boddy K, Dawes GS, Fisher R, Pinter S and Robinson JS. (1974): Foetal respiratory movements, electrocortical and cardiovascular responses to hypoxemia and hypercapnia in sheep. J.Physiol. 243:599.

7. Natale R, Clewlow F and Dawes GS. (1981): Measurement of fetal forelimb movements in the lamb in utero. Am. J. Obstet. Gynecol. 140:545.

8. Wood C, Hammond J, Lumley J and Newman W. (1971): Effect of maternal inhalation of 10% oxygen upon the human fetus. Aust. N.Z. J. Obstet. Gynaec. 11:85.

9. Itskovitz J, Goetzman BW and Rudolph AM. (1982): The mechanism of late deceleration of the heart rate and it's relationship to oxygenation in normoxemic and chronically hypoxemic fetal lambs. Am. J. Obstet. Gynecol. 142:66.

10. Huch A, Huch R, Schneider H and Rooth G. (1977): Contineous transcutaneous monitoring of fetal oxygen tension during labour. Br. J. Obstet. Gynaecol. 84: suppl. 1-39.

11. Dawes GS, Visser GHA, Goodman JDS, and Redman CWG. (1981): Numerical analysis of the human fetal heart rate : The quality of ultrasound records. Am. J. Obstet. Gynecol. 141:43.

12. Harding R, Poore ER and Cohen GL. (1981): The effect of brief episodes of diminished uterine blood flow on breathing movements sleep states and heart rate in fetal sheep. J. Develop. Physiol.3:231.

13. Boddy K and Dawes GS. (1975): Fetal breathing. Br. Med. Bull. 31:3.

14. Dornan JC and Ritchie JWK. (1983): Fetal breathing movements and maternal hyperoxia in the growth retarded fetus. Br. J. Obstet. Gynaecol. 90:210.

15. Wilkinson C and Robinson J. (1982): Braxton Hicks contractions and fetal breathing movements. Aust. N.Z. J. Obstet. Gynaecol. 22:212.

16. Nijhuis JG, Prechtl HFR, Martin CB and Bots RSGM. (1982): Are there behavioural states in the human fetus? Early Hum. Dev. 6:177.

17. Visser GHA, Heringa MP, Mulder EJH and Bekedam DJ. (1984): Effects of prolonged uterine contractions, associated with fetal heart rate decelerations on human fetal behavioural states. Abstr. 2nd Conference Fetal and Neonatal physiological measurements, Rolfe P, ed. Expres Litho Service,Oxford, k4.

18. Martin CB, v/d Wildt B, Slaitsch KJ and Jongsma HW. (1983): Intermittent reduction of uterine blood flow can modulate behavioural state in sheep. Society for Gynecological Investigation, 30th meeting, Washington, p297.

5

THE EFFECTS OF MATERNAL HYPEROXIA ON FETAL BREATHING MOVEMENTS, BODY MOVEMENTS AND HEART RATE VARIATION IN GROWTH-RETARDED FETUSES

Introduction

In compromised intrauterine growth-retarded fetuses (IUGR) a reduction in the incidence of fetal breathing and body movements has been observed, as well as a reduction of long-term heart rate variation. [1,2,3,4,5] These findings are associated with fetal hypoxaemia and a causal relationship has been suggested. [3,4,6] If this is so, then one would expect this effect to be abolished by increasing the fetal pO_2. Such an increase in fetal oxygen tension can be achieved by maternal hyperoxygenation. [7] As far as fetal breathing and body movements are concerned, an increase has in fact been found in IUGR fetuses during maternal hyperoxia. [8,9]

In this study, we investigated the effect of maternal hyperoxygenation on fetal body and breathing movements, as well as on heart rate variation in growth-retarded fetuses. Control data were obtained from a group of appropriately grown fetuses. Such a study is of even more interest as maternal hyperoxygenation is considered to be a mode treatment for severe IUGR [7]; an effect on fetal movements and heart rate variation could therefore be of clinical use to monitor changes in fetal condition.

Patients and methods

Fetal breathing, body movements and heart rate variation were studied in 16 patients admitted with suspected intrauterine growth retardation and in 13 women with uncomplicated pregnancies. All IUGR fetuses had abnormal umbilical artery Doppler velocity waveform patterns, indicative of uteroplacental insufficiency. At delivery, all had a birth weight below the 10th percentile (corrected for sex, parity and gestational age according to the Dutch Kloosterman curves). The control group consisted of 13 uncompli-

cated pregnancies with birth weights above the 25th percentile. Clinical data on the study and control groups are shown in Table 1.

Recordings were made between 1400 and 1700 hours, two hours after a meal, with the patient in a comfortable semirecumbent position. In the study group of 16 patients, 19 recordings were made, whereas 13 were made in the control group. Each 2-hour recording consisted of a control period of 40 minutes, followed by 40 minutes of maternal oxygen administration by means of a face mask with 50% oxygen at a flow rate of 9 liters per minute. The recording was continued for another 40 minutes following the discontinuation of oxygen administration. In 6 patients, maternal transcutaneous pO_2 and pCO_2 were measured continuously (Radiometer TCM2). After calibration, the combined pO_2 and pCO_2 electrode was applied to the maternal chest just above the clavicula.

Table 1
Clinical data on the IUGR group and control group.

	IUGR n=16	Control n=13
Mean age (in years)	29.5	27.6
Mean gestational age		
- at recording (wk)	32.0	32.0
(range)	(27.3-38.6)	(28.1-36.5)
- at birth (wk)	33.3	40.3
(range)	(28.3-39.1)	(36.5-42.2)
PIH (n)	8	0
Antihypertensive drugs (n)	3	0
Abnormal umb. art. PI (n)	16	0
Mode of delivery (n)		
- vaginal	1	12
- CS	15	1
Mean birth weight (g)	1257	3635
(range)	(550-2530)	(2770-4280)
Umb. art. pH (mean)	7.23	7.21
Apgar score (mean)		
- 1 min	7.3	8.4
- 5 min	8.8	9.7

Fetal breathing and body movements were observed with a real time linear-array ultrasound scanner (Aloka, Model SSD-256) and were recorded by means of an event-marker on a 4-channel recorder (Hewlett-Packard, 7754A). For fetal breathing movements, apnoea was defined as a pause between two breaths of >6 seconds. The incidence of fetal breathing was expressed as a percentage of the recording time. Body movements occurring within 5 seconds of each other were considered to be a single movement and their incidence was also expressed as a percentage of the recording time.

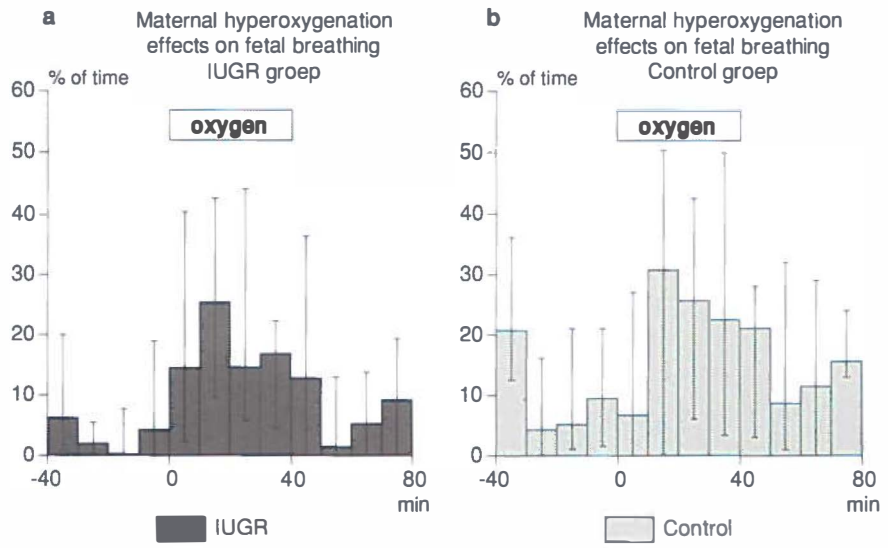
Fetal heart rate (FHR) was recorded simultaneously with a Doppler ultrasound transducer (Hewlett Packard cardiotocograph Model 8040A). The records were analysed visually for the occurrence of late heart rate decelerations. In 12 recordings of the IUGR group and in all 13 recordings of the control group, FHR variation was analysed numerically, using an on-line microprocessor system, as described previously. [10] With this system, first a baseline was fitted to the fetal heart rate trace. Subsequentely, accelerations (>10 bpm lasting >15 seconds) and decelerations (>10 bpm lasting >60 seconds, or >20 bpm lasting >30 seconds) were identified and heart rate variation was measured. As to the latter, the range of mean pulse intervals about the baseline is calculated minute by minute, excluding the decelerations. These values were averaged to give a measure of long-term heart rate variation ("mean minute range" in msec).

Results are presented as medians and interquartile ranges (iqr), unless stated otherwise. Statistical analysis was performed with the Wilcoxon matched-pairs signed rank test. The significance levels are given for two-sided tests.

Results

Maternal hyperoxygenation

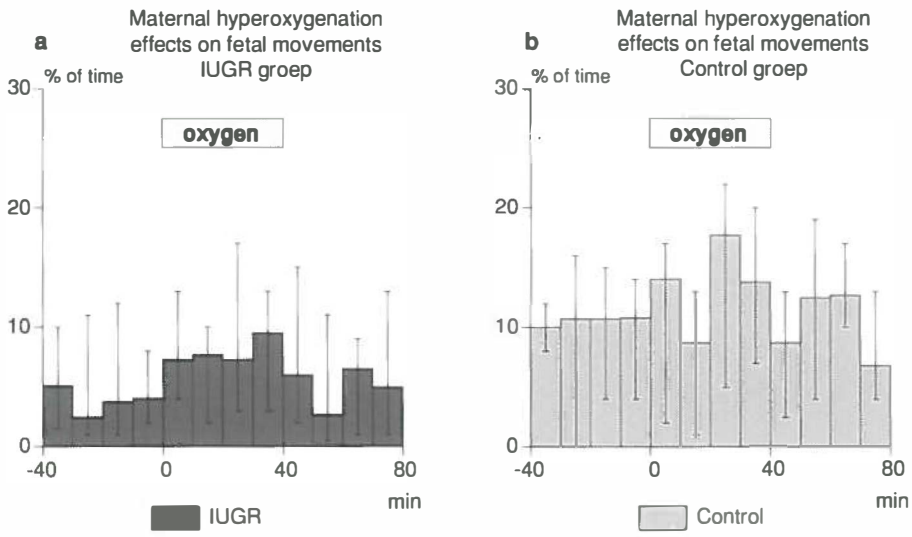
Transcutaneous pO_2 and pCO_2 levels were measured in 6 women. In the control period prior to maternal hyperoxygenation the mean transcutaneous pO_2 was 74 +4.3 mm Hg. Within 5 minutes after the onset of oxygen inhalation the pO_2 levels reached to plateau values (mean 171+8.4 mm Hg). Within 5 minutes after discontinuation of hyperoxygenation, the transcutaneous pO_2 returned to baseline levels (83 +3.4 mm Hg). Transcutaneous pCO_2 values were not found to be significantly different before, during or after the procedure (29.5 +0.4, 29.7 +0.5 and 29.8 +0.5 mm Hg, respectively).



Figs 1a and 1b
The percentages of time in which fetal breathing movements were present, per 10 min epoch, in both IUGR (n=16, 19 recordings) and control fetuses (n=13). During 40 minutes of maternal hyperoxygenation the median fetal breathing movement incidence increased from 7.0% to 17.4% of time in the IUGR fetuses ($p< 0.005$, Fig. 1a). In the control group there was also an increase in the fetal breathing incidence, however, this did not reach significance (median value: 8.7% to 21.6% of time, $p=0.07$, Fig. 1b).

Fetal breathing movements

In the IUGR group, the median incidence of fetal breathing increased significantly from 7.0% (iqr=15.7%) of time before hyperoxygenation to 17.4% (iqr=35.2%) during hyperoxygenation ($p<0.005$) (Fig. 1a). Thereafter the time spent breathing decreased to 13.4% (iqr=15.7%) ($p<0.05$). The increase in breathing movements was not found uniformally, as no increase was noted in 4 out of the 19 recordings. In the control group, the median incidence of fetal breathing rose from 8.7% (iqr=20.9%) to 21.6% (iqr=40.1%); this increase, however, did not reach statistical significance ($p=0.07$) (Fig. 1b). In the 40 minutes after the oxygen inhalation, the median breathing incidence in this group decreased to 10.5% (iqr=15.7%) of the time.



Figs 2a and 2b
The percentages of time fetal body movements were observed in IUGR and control fetuses. In IUGR fetuses, there was an increase in fetal body movements during hyperoxygenation from a median value of 6.1% to 7.9% of time ($p<0.05$ Fig. 2a). No increase in fetal body movements was found in the control group (median value: 11.5% to 11.7% ns, Fig. 2b).

Fetal body movements

In the IUGR group an increase occurred in 14 out of the 19 hyperoxygenation experiments. There was a small, but significant increase in the incidence of fetal body movements between the control period and the hyperoxygenation period; 6.3% (iqr=8%) to 7.9% (iqr=10.2%) ($p<0.05$) (Fig. 2a). Afterwards the median incidence of fetal body movements was 7.7% (iqr=8.25%). In the control group no significant differences were found between the median fetal movement incidence before, during or after hyperoxic stimulation; (11.7% (iqr=11%), 11.9% (iqr=8.4%) and 10.5% (iqr= 5.25%), respectively) (Fig. 2b).

Fetal heart rate and heart rate variation

In the 12 recordings of the IUGR group that were analysed numerically, there was a significant increase in long-term heart rate variation during hyperoxygenation (percentage increase of 18.5%, $p<0.05$). After the discontinuation of oxygen inhalation, the level of heart rate variation decreased to baseline values. (Fig. 3). Mean basal fetal heart rate did not change signifi-

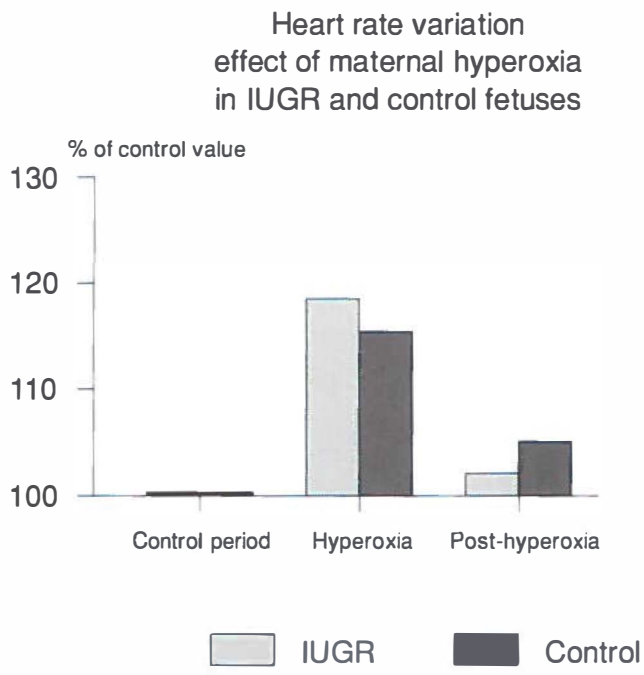
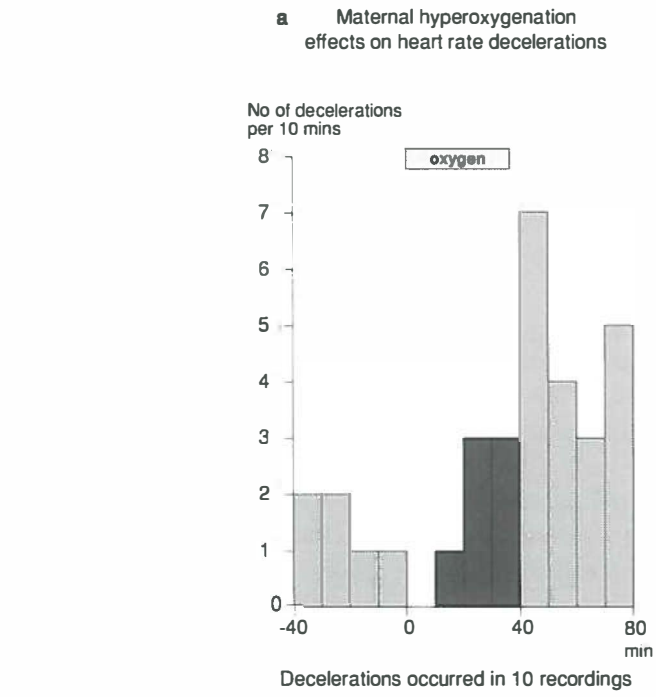


Fig. 3
Both in the IUGR group and in the control group, there was a significant increase in heart rate variation during maternal hyperoxygenation. The percentage increase of the mean minute range during and after oxygen administration as compared to the preceding control period is shown.

cantly during or after maternal hyperoxygenation 141.7, 140.1 and 140.8 beats per minute, respectively. Heart rate variation also increased in the control group. The mean increase was 15.5% as compared to the pre-hyperoxygenation values (Fig 3. $p<0.05$). In the control group mean basal fetal heart rate decreased slightly during oxygen administration from 136.8 to 132.0 beats per minute remaining at 130.0 beats per minute afterwards.

The heart rate traces were analysed visually for the occurrence of heart rate decelerations of >20 beats per minute with a duration of 60 seconds or more. Thirty-two decelerations occurred in 10 of 19 recordings in the IUGR group, while no decelerations were found in the control group. When decelerations occurred they were predominantly present in the period after maternal hyperoxygenation (Figs 4a and 4b). No decrease in the number of decelerations was found during oxygen administration as compared to the preceding control period.



Figs 4a and 4b
Heart rate decelerations (n=32) were present in 10 of the study group recordings. The decelerations were predominantly present after discontinuation the oxygen administration; Fig 4a. An example is demonstrated in Fig. 4b

Discussion

In the growth-retarded fetuses, we found an increase in the fetal breathing incidence during maternal hyperoxgenation. This is in accordance with the findings of others. [8 9] Recently, cordocentesis data have shown that maternal hyperoxygenation indeed increases fetal pO_2 levels in IUGR fetuses. [7] It is

therefore appropriate to assume that the increase in fetal breathing movements is caused by the rise in fetal pO_2, especially as no increase in the maternal transcutaneous pCO_2 was found. However, this does not exclude the possibility that hyperoxygenation does increase aerobic metabolism, which in turn releases tissue carbon dioxide and has a consequential stimulatory effect on fetal breathing movements. Another possibility is that increased oxygen tension stimulates fetal breathing through a direct effect on the supramedullary brain stem by abolishing the hypoxaemic inhibition of fetal breathing movements. [11 12]

In IUGR fetuses, the incidence of fetal body movements is reduced below the normal range when antepartum FHR decelerations are present and heart rate variation is reduced. [3] This situation is associated with fetal hypoxaemia and sometimes mild acidaemia, as determined in cord blood at Caesarean section or by cordocentesis. [3 6] The increase in fetal body movements in IUGR fetuses during hyperoxygenation substantiates the suggestion that in growth-retarded human fetuses a causal relationship exists between a reduction of fetal movements and fetal hypoxaemia. The reduction of fetal activity may be considered as one of the compensatory mechanisms to the decrease of oxygen supply. Fetal sheep studies have shown that fetal movements consume a significant amount of oxygen. The abolition of fetal movements by gallamine or curare derivates, leads to a decrease in fetal oxygen consumption and an increase in vascular pO_2. [13 14] However, it is likely that a reduction of fetal movement occurs late in the process of fetal deterioration because oxygen consumption is maintained during the initial decrease of oxygen delivery, probably due to increased oxygen extraction. [15 16] Clinically, this is illustrated by the fact that in IUGR fetuses the fetal movement incidence is generally within the (lower) normal range and only falls below the normal range when late heart rate decelerations occur . [3]

In the IUGR fetuses, there was also a slight, but significant increase in heart rate variation during hyperoxic stimulation, although variation remained lower than in the control group. This indicates that fetal oxygen tension levels (at least partly) mediate heart rate variability and supports earlier findings of an association between pO_2 and heart rate variation in IUGR. [3 5] Thus, the measurement of fetal heart rate variation over longer periods may identify fetuses developing hypoxaemia.

Although maternal hyperoxygenation was associated with an increase in heart rate variation, it did not result in a reduction of the number of heart rate decelerations. Furthermore, the increase of decelerations after discontinuation of oxygen was an unexpected adverse effect. This might be due to the inadequate redistribution of the cardiac output after discontinuation of

the maternal hyperoxygenation. Animal experiments have shown that a reduction in oxygen supply results in the redistribution of blood flow in favour of the brain and myocardium. Also in the human IUGR fetus, changes in blood velocity waveform patterns have been described indicating a decrease in the vascular resistance of the brain. [16] This redistribution can be abolished by the administration of oxygen to the mother . [17] The sudden discontinuation of oxygen administration leaves the fetus, temporarily, in a state of increased metabolic activity and with relatively high vascular resistance of the brain. This might result in "critical" hypoxaemia and in an increase of heart rate decelerations. Only when oxygen consumption has decreased, will adequate adaptation be restored.

Recently Nicolaides et al. (1987) have described long-term maternal oxygen administration as a therapy for severely growth-retarded fetuses. [7] They found an increase of fetal pO_2 within the normal range in all the 5 patients studied; the neonatal outcome was favourable. We found a beneficial effect of short-term maternal hyperoxygenation on fetal movements and heart rate variation. The temporary increase in the number of heart rate decelerations after the discontinuation of oxygen indicates, that when such a "therapy" is being considered, oxygen should be administered continuously, i.e. without interruption. However, the possible benefit of maternal oxygen therapy still has to be investigated in a prospective randomized trial.

We were slightly puzzled by the increase in fetal breathing incidence during hyperoxygenation in the control group, although this increase was not statistically significant. The start of maternal hyperoxygenation was more than 2 1/2 hours after the last meal and one would expect a decrease in the incidence of breathing, in relation to decreasing blood glucose levels, rather than an increase. [18] Reviewing the literature, it appeared that in all 5 studies in which the effect of maternal hyperoxygenation was investigated in uncomplicated pregnancies, a slight but non-significant increase in fetal breathing incidence was reported. [8 9 19 20 21] In the present study, there was also an increase in heart rate variation in the control fetuses during maternal oxygen inhalation. If this increase is caused by the rise in fetal oxygen tension and not by concomitant factors, it suggests that changes in pO_2 may have an effect on the fetal activity state in the normoxaemic fetus. It has been reported that fetal breathing movements are predominantly present in fetal behavioural state 2F [22] and this could explain the rise in fetal breathing incidence seen in control fetuses in this study. Also, in fetal sheep, an increase in arterial oxygen tension combined with lung distension was found to induce continuous fetal breathing . [23 24] It is still unclear, what effect fetal pO_2 levels of well above the physiological range have on the control of breathing.

In conclusion, in IUGR fetuses, heart rate variation and movement incidence were found to fall below the normal range in the case of fetal hypoxaemia. [3] The increase in heart rate variation and in fetal breathing and body movements during maternal hyperoxygenation observed in IUGR fetuses, further substantiates the relationship between these variables and the oxygenation status of the fetus.

Acknowledgements

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References

1. Boddy K, Dawes GS. (1975): Fetal breathing. Br. Med. Bull. 85:787.

2. Bekedam DJ, Visser GHA, de Vries JJ, Prechtl HFR. (1985): Motor behaviour in the growth retarded fetus. Early Hum. Dev. 12:155.

3. Bekedam DJ, Visser GHA, Mulder EJH, Poelmann-Weesjes G. (1987): Heart rate variation and movement incidence in growth-retarded fetuses: The significance of antenatal late heart rate decelerations. Am. J. Obstet. Gynecol. 157:126.

4. Henson GL, Dawes GS, Redman CWG. (1983): Antenatal fetal heart rate variability in relation to fetal acid-base status at caesarean section. Br. J. Obstet. Gynaecol. 90:516.

5. Smith JH, Anand KJS, Cotes PM, Dawes GS, Harkness RA, Howlett, TA, Rees LH, Redman, CWG. (1988): Antenatal fetal heart rate variation in relation to the respiratory and metabolic status of the compromised human fetus. Br. J. Obstet. Gynaecol. 95:980.

6. Visser GHA, Sadovsky G, Nicolaides KH. (1989): Antepartum heart rate patterns in small-for-gestational age third trimester fetuses: Correlations with blood gases obtained at cordocentesis. Am. J. Obstet. Gynecol. in press.

7. Nicolaides KH, Bradley RJ, Soothill PW, Campbell S, Bilardo CM, Gibb D. (1987): Maternal oxygen therapy for intrauterine growth retardation. Lancet 942.

8. Dornan JC, Ritchie JWK. (1983): Fetal breathing movements and maternal hyperoxia in the growth retarded fetus. Br. J. Obstet. Gynaecol. 90:210.

9. Ruerich DA, Devoe LD, Searle N. (1989): Effects of maternal hyperoxia on the biophysical assessment of fetuses with suspected intrauterine growth retardation. Am. J. Obstet. Gynecol. 161:188.

10. Dawes GS, Redman CWG, Smith JH. (1985): Improvements in the registration and analysis of heart rate records at the bedside. Br.J Obstet. Gynaecol. 92:317.

11. Dawes GS, Gardner WM, Johnston BM, Walker DW. (1983): Breathing in fetal lambs; the effect of brain stem section. J. of Physiol. 335:535.

12. Koos BJ, Sameshima H. (1988): Effects of hypoxemia and hypercapnia on breathing movements and sleep state in sinoaortic-denervated fetal sheep. J. of Develop. Physiol. 10:131.

13. Rurak DW, Gruber NC. (1983): The effect of neuromuscular blockade on oxygen consumption and blood gases in the fetal lamb. Am. J. Obstet. Gynecol. 145:258.

14. Nathanielz PW, Yu HK, Cabalum TC. (1982): Effect of abolition of fetal movement on fetal intravascular PO_2 and incidence of tonic myometrial contractures in the pregnant ewe at 114 to 134 days' gestation. Am. J. Obstet. Gynecol. 144:614.

15. Wilkening RB, Meschia G. (1983): Fetal oxygen uptake, oxygenation and acid-base balance as a function of uterine blood flow. Am.J. Physiol. 244:749.

16. Wladimiroff JW, Tonge HM, Stewart PA. (1986): Doppler ultrasound assessment of cerebral blood flow in the human fetus. Br. J. Ostet. Gynaecol. 93:471.

17. Arduini A, Giuseppe R, Mancuso S, Romanini C. (1988): Short-term effects of maternal oxygen administration on blood flow velocity waveforms in healthy and growth-retarded fetuses. Am. J. Obstet. Gynecol. 159:1077.

18. Patrick J, Campbell K, Carmichael L, Natale R, Richardson B. (1980): Patterns of human fetal breathing during the last 10 weeks of pregnancy. Obstet.Gynecol. 56:24.

19. Richtie JWK, Lakhani K. (1980): Fetal breathing movements and maternal hyperoxia. Br. J. Obstet. Gynaecol. 87:1084.

20. Devoe LD, Abduljabbar H, Carmichael L, Probert C, Patrick J. (1984): The effects of maternal hyperoxia on fetal breathing movements in third-trimester pregnancies. Am. J. Obstet. Gynecol. 148:790.

21. Van Vliet MAT, Creemers HMH, van Heyst AFJ, Martin CB. (1985): The effect of maternal hyperoxia on breathing movements, body movements and rest-activity cycles of low-risk human fetuses. Europ. J. Obstet. Gynecol. Reprod. Biol. 20:221.

22. Van Vliet MAT, Martin CB, Nijhuis JG, Prechtl HFR. (1985): The relationship between fetal activity and behavioral states and fetal breathing movements in normal and growth-retarded fetuses. Am.J. Obstet. Gynecol 153:582.

23. Blanco CE, Moertzdorf W, de Jong D, Pfaff L, Hanson M. (1989): Effects of changes in fetal oxygenation on fetal breathing activity. Abstract Soc. for the Study of Fetal Physiology, Reading, England, July 1989.

24. Hasan SU, Salkauskas A, Alston JT, Dascalu VI. (1989): The effects and interrelation of lung distension, oxygenation and gestational age on fetal breathing movements in sheep. Abstract Soc. for the Study of Fetal Physiology, Reading, England, July 1989, G7.

6

MOTOR BEHAVIOUR IN THE GROWTH-RETARDED FETUS

Summary

In 10 intrauterine growth-retarded fetuses (IUGR) a qualitative and quantitative analysis was made of various movement patterns. The results were compared to those of 10 matched appropriate-for-gestational age fetuses (AGA). The aim of the study was to see whether malnourished, growth retarded fetuses move differently from well-nourished, normal fetuses. The real-time ultrasound recordings were of one hour's duration and the analysis of motility was carried out during replay of video-recordings. The qualitative analysis of each separate general movement was performed with "Gestalt perception" describing the speed, force and amplitude of each movement as well as the variability of these descriptors. Interobserver agreement was evaluated by displaying general movements in both groups to 8 observers. There was an overall interobserver agreement of 89%.

The IUGR fetuses moved less, but in individual cases an overlap existed with control fetuses. There was a reduction in both number and duration of general movements in the IUGR group: Furthermore, the markedly reduced incidence of startles, twitches and isolated limb movements was striking. The qualitative analysis of general movements revealed a reduction in the quicker components leading to slow and monotonous movement patterns. There was also a marked reduction in variability of speed and intensity within each movement pattern. We speculate that the reduced variability of motor patterns may find its origin in a change of central neural function, just as the reduced heart rate variability and decreased breathing irregularity found in IUGR fetuses.

Introduction

Gruenwald's study[6] on reduced utero-placental circulation led to the concept of "fetal malnutrition" and to the identification of infants who are "small for gestational age". The majority of these growth retarded fetuses have one main variable in common: "the reduced supply line". Since then, a few authors have investigated the effects of this metabolic deprivation on neona-

tal neurological development.[8 10 12 19] Although a relative sparing of brain weight compared to body weight has been found[6], detrimental effects on brain histology and chemical composition have also been reported.[1 4] Whether or not these deviations in neural development find their expression in the function of the fetal nervous system is still speculative. As fetal motility is a direct indicator of the functional condition of the nervous system, a detailed investigation on fetal movement patterns may provide an answer.

The question of how fetal motility should be assessed raises an essential point in fetal studies: the distinction between "quantity" and "quality" of fetal motor patterns. Quantity is the amount of fetal movements, either perceived by the mother or recorded mechanically or by ultrasound imaging. These data are expressed as a percentage of the observation time or as the number of events per time epoch. The non-imaging methods are rather insensitive as many small movements are missed and no distinction can be made between different movement categories. With visualization of the fetus, different movement patterns can be distinguished and their incidence and temporal sequence can be analysed.[23 24] In addition, the quality of each individual movement can now be appreciated. This requires "Gestalt perception" by the observer, which is a perceptual process whereby observable properties of each specific movement pattern, such as speed, amplitude and force, are combined in one complex perception.

As the qualitative approach requires extensive knowledge of normal motility patterns, most studies have concentrated on the incidence of one or two movement categories hoping thereby to be able to identify the compromised fetus. Reduction or cessation of fetal movements is a late and alarming sign heralding impending intrauterine death and coincides with fetal hypoxaemia.[2 17] With less severe degrees of compromise, intra-individual fluctuations and inter-individual differences in movement incidence, blur the distinction between the normal and abnormal fetus.

Inter-individual differences in the quantity of spontaneous motor output has also been found in prematurely born infants. Prechtl and Nolte[13] investigated normal and neurologically impaired preterm infants. Except for a higher incidence of cloni in the abnormal group, there was no marked difference in the quantity of the different motor patterns studied. However, video analysis of another group of sick preterm infants revealed a "reduction of elegance and fluency, as well as variability, fluctuation in intensity and speed rather than any change in incidence of distinct motor patterns".[13,p89]

Owing to the fact that prolonged malnutrition may cause deviations in the functional expression of the nervous system, as already discussed, we compared motility in the growth retarded and normal fetus to investigate the following question: Do the quality and quantity of fetal movements in fetuses

with signs of impaired growth due to chronic malnutrition differ from those in well-nourished normal fetuses?

Patients and Methods

The study group consisted of 10 growth retarde- fetuses identified in pregnant women admitted to the obstetrical ward with the clinical diagnosis of intrauterine growth retardation, associated in nine of the ten cases with pregnancy-induced hypertension (PIH). All women had singleton pregnancies and reliable pregnancy dates. Fetuses suspected of having an intrauterine infection or a congenital anomaly were excluded from the study. Clinical data are summarized in Table 1. Continuous real-time ultrasound recordings of one hour were made with a linear array scanner (Aloka 256sd). The transducer was positioned in a para-sagittal plane visualizing the upper part of the fetal abdomen, the fetal thorax, mouth and one orbit. All recordings were performed between 16.00 and 19.00 hrs, with the women lying in a comfortable semi-recumbent position, slightly tilted to the left. The scanning images of each session were recorded on videotape for off-line analysis. Two observers recorded general movements, breathing, mouth and eye move-

Table 1
Clinical data of the pregnancies in the study group

case no.	age (yrs)	parity	obstetrical complications*	position	drugs**
1	33	1	PIH, alb.,haem.	transverse	no
2	35	2	PIH, alb.	vertex	yes
3	23	1	PIH, haem.	vertex	yes
4	31	1	PIH	transverse	yes
5	28	0	PIH	vertex	no
6	20	0	none	breech	no
7	28	2	PIH	vertex	no
8	21	0	PIH	vertex	no
9	22	0	PIH, alb.	vertex	no
10	22	0	PIH	vertex	no

* PIH = pregnancy induced hypertension, alb.=albumuria, haem.=third trimester antepartum haemorrhage.
** anti-hypertensive drugs.

ments on-line on a 4-channel recorder (HP 7754A) by means of push buttons. These data were stored on magnetic tape (Philips Analog-7). Fetal heart rate was recorded simultaneously with a cardiotocograph (HP 8030A), using a phonomagnetic or abdominal ECG signal and stored on magnetic tape.

Extensive analysis of fetal motility was carried out during playback of the video recordings. The different movement categories were defined according to descriptions of motor patterns seen in the full-term and preterm infant[13,14] as well as in the fetus in the first half of gestation.[23] A description is presented in Table 2. The incidence, duration and sequence over time of the different movement categories were noted and represented as an actogram. Qualitative analysis of each separate general movement was performed, describing observable properties of each movement, such as speed, force and amplitude, as well as the variability and fluctuation of these parameters. Each parameter was scored as normal, moderately reduced, markedly reduced or absent. The overall impression of each general movement was scored as normal, suspect or abnormal.

Table 2
Definition of some movement patterns

General movements: Series of gross movements of variable speed and amplitude which involve all parts of the body, but no distinctive patterning or sequencing of body parts can be seen. Despite this lack of clear patterning, they can be easily recognized as a separate category. Duration varies from a few seconds to about a minute.
Isolated arm movements: Rapid or slow movements involving flexion, extension, rotation or abduction and adduction of the arm and hand without movements of any other body part.
Startles: Quick generalized movements, always starting in the limbs and sometimes spreading to the neck and trunk. Movements last about one second.
Twitches: Isolated rapid movements of limb or head. They differ from startles in not being generalized.
Head movements: Isolated rotations and retroflexions of the head not associated with general movements.
Breathing movements: Fluent caudal movements of the diaphragm leading to movements of the thorax (inwards) and abdomen (outwards).

Ten healthy women with uncomplicated, reliably dated pregnancies acted as controls. The same recording procedures were performed and the gestational age at the time of the recording was matched to that of the study group. Examples of one-hour actogrammes of a growth-retarded fetus and a control fetus are shown in Fig. 1.

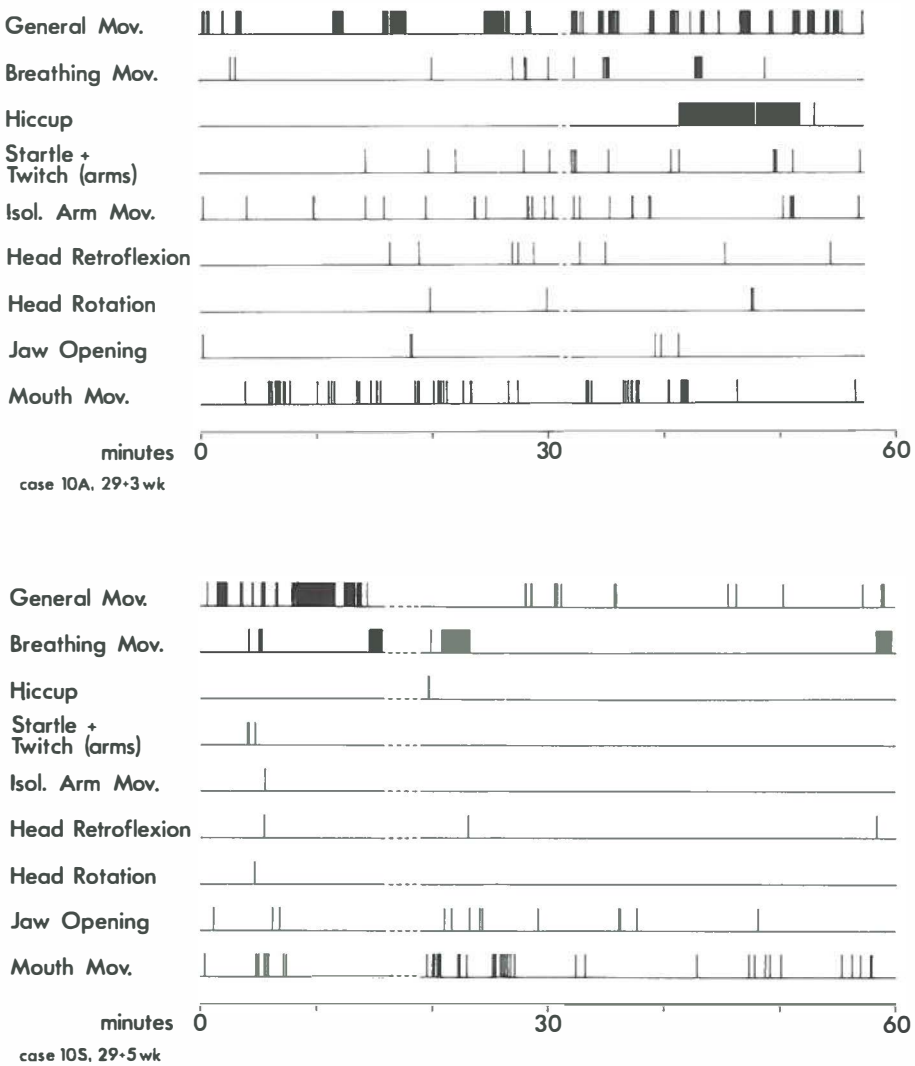

Figure 1
Examples of one-hour actogrammes of a control fetus (case no.10A, 29+3 wks) and a growth-retarded fetus (case no.10S, 29+5 wks).

Table 3
Obstetrical and neonatal data on the study group

Case no.	Gestational age at		Sex	Birth weight and percentile		Umbilical pH		Apgar score	
	rec.	birth				pH_{ua}	pH_{uv}	1 min	5 min
1	30+1	30+5	f	890	< 5	7.21	7.27	1	5
2	31+4	31+5	f	1230	< 10	7.24	7.32	9	10
3	30+5	30+6	m	1240	< 10	7.17	7.18	5	9
4	28+4	29+1	f	610	< 2.3	7.24	7.27	7	10
5	33+3	33+4	f	1080	< 5	7.20	7.27	8	10
6	35+0	35+1	f	1250	< 2.3	7.27	7.32	7	10
7	33+3	33+4	f	1275	< 10	7.26	7.32	8	10
8	35+2	35+2	f	1100	< 2.3	7.15	7.18	1	7
9	30+5	30+6	m	960	< 2.3	7.26	7.29	7	9
10	29+5	30+5	m	890	< 2.3	-	7.23	1	6

rec = recording

Data on the distribution of the observations with respect to gestational age, the gestational age at delivery and postnatal findings of the study group are presented in Table 3.

All infants in the study group were delivered by elective Caesarean section, performed because of suspected fetal compromise. Nine fetuses had decelerative heart rate tracings prior to Caesarean section[22] (the exception was case no. 6.). The infants of control group mothers were delivered vaginally. The birth weights of these infants were all above the 25th percentile.[9]

The amount of amniotic fluid was evaluated subjectively. It was reduced in all pregnancies with fetal growth retardation; in three cases oligohydramnios was marked, in the other seven it was mild. In the control group, the amount of amniotic fluid was normal in all cases.

Interobserver agreement was evaluated by displaying 40-second episodes of general movements of both groups to 8 experienced observers. Observations of speed, amplitude and force as well as the variabilty of these parameters were scored as normal, suspect or abnormal. The general impression of each movement was also scored. Despite the severity of this testing (40-second episode, only one general movement per case) there was an overall

Table 4
Interobserver agreement in the distinction of normal and abnormal movement quality in five appropriate-for-gestational age (AGA) and five growth-retarded fetuses(IUGR)

	AGA					IUGR				
	A	B	C	D	E	F	G	H	I	J*
Movement quality										
normal	8	8	8	8	8	1	-	-	-	6
suspect	-	-	-	-	-	1	2	2	1	1
abnormal	-	-	-	-	-	6	6	6	7	1

No. of observers=8.
* Growth-retarded fetus with normal motor activity (case no. 6).

inter-observer agreement of 89%. All observers were unanimous in recognizing the normal movement quality of the appropriate-for-dates fetuses. There were only two major disagreements in the observations of the growth-retarded fetuses; one abnormal movement pattern was scored as normal by one observer, whereas one normal movement pattern was scored abnormal by one other observer. Results are displayed in Table 4.

Neurological examination was performed in 9 of the 10 growth-retarded infants and in all control infants between 40 and 52 weeks post menstrual age. The general outcome of the neurological assessment was favourable. Three of the growth-retarded infants showed minor neurological symptoms, (i.e. two were hyperexcitable, one was mildly hypertonic) whereas one of the control infants showed signs of a mild hypotonia. All results are presented as medians and ranges unless stated otherwise. The Wilcoxon matched pairs signed rank test (two-tailed) was used to assess significant differences between both groups.

Results

The incidence of each movement is reported per category for both groups of fetuses in this section.

General movements Fig. 2
The median percentage of time general movements were present was significantly lower in the group of growth-retarded fetuses (10.7% vs. 4.0%, $p<0.01$.) However, four cases overlapped the range of the controls. The number of general movements as well as the median duration of each general movement was reduced ($p<0.01$).

Startles and Twitches Fig. 3
These were combined into one figure, because differentiation was often difficult as the fetuses were not fully visualized. In the growth-retarded fetus, these quick and brisk movements were significantly reduced ($p<0.01$).

Isolated arm movements Fig. 3
A distinct reduction was found in the number of isolated arm movements in the growth-retarded fetuses ($p<0.01$).

Isolated head retroflexions Fig. 4
These movements were not reduced in the growth retarded fetuses.

Isolated head rotations Fig. 4
These movements were significantly lower in the study group ($p<0.05$)

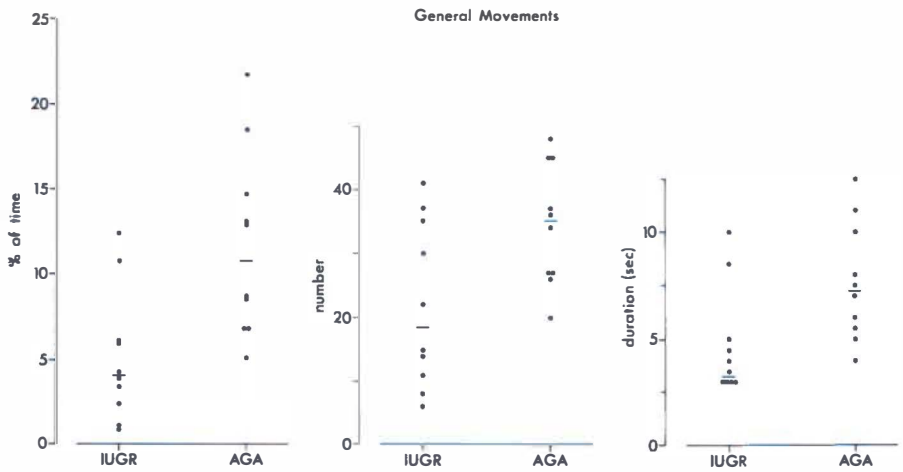

Figure 2
The median incidence of general movements expressed as % of time and number of movements and the median duration of each general movement in the study group (IUGR) and control group (AGA)

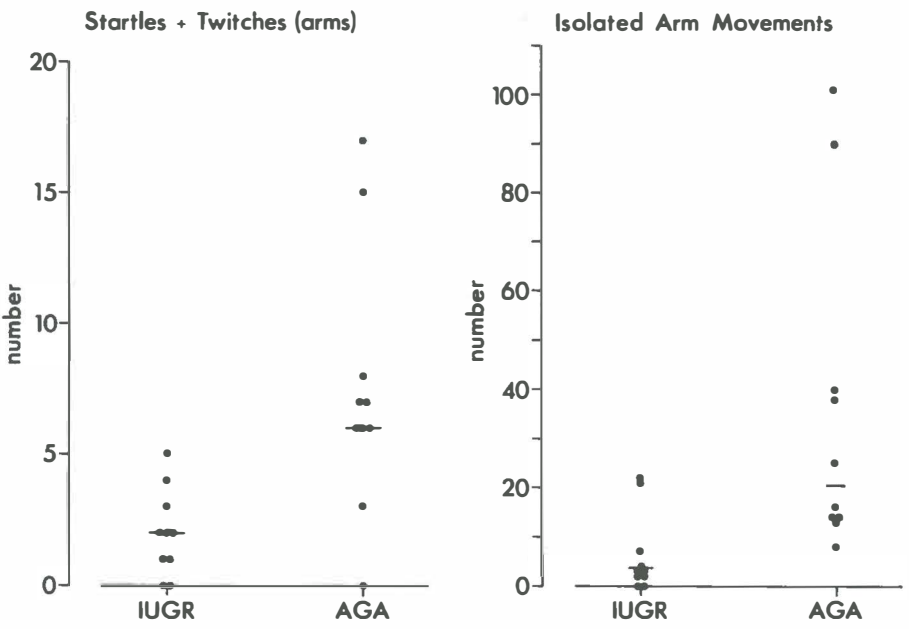

Figure 3
Number of startles + twitches (arms) and isolated arm movements in the growth-retarded group (IUGR) and control group (AGA)

Breathing movements Fig. 5
The median percentage of time spent breathing was not significantly lower in the study group than in the control group ($p<0.05$).

Although there were significant quantitative differences in motor output between both groups, overlaps existed for most categories. However, analysis of the movement quality revealed distinct differences between the groups. In the normal fetus, movements were complex and variable in composition, speed and intensity. Much in contrast to this, a general monotony of movement patterns was noted in all but one of the growth-retarded fetuses (case no. 6 was the exception). The movements were slow, lacked power and amplitude and were characterized by a striking reduction in variability of intensity and speed, leading of the disappearance of the normal waxing and waning of the movement. Although parameters such as speed, power and amplitude were reduced, it must be emphasized that the overall monotony was the most impressive feature. This was also observed in the isolated movements. Subtle movements of the arm and hand, varying in speed and intensity, were seen only in the normal fetuses. The head movements, both iso-

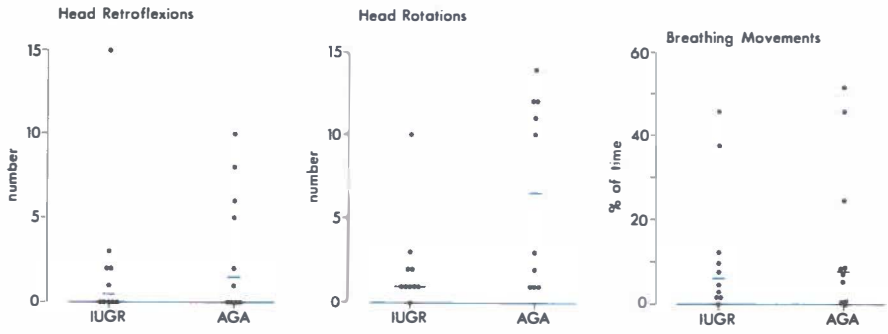

Figure 4
Number of isolated head movements in the growth retarded group (IUGR) and control group (AGA)

Figure 5
Breathing movements as % of time in study and control groups

lated or as components of general movements are another example. They were performed slowly with small amplitude in the growth-retarded fetus, as if the movements were not fully executed. Although the above-described pattern was characteristic for the group as a whole, apart from case no. 6 inter-individual differences in performance existed.

The position of the fetus did not seem to influence the movement quality. There were no differences between fetuses in vertex or breech position in either group. Positional changes, such as rotations around the longitudinal axis, were seen more often in the control group than in the growth retarded fetuses. The posture of the growth-retarded fetus was slightly more crouched. The vertebral column had a tendency to be more flexed, especially at cervical level.

Discussion

This study showed differences in motor behaviour between growth-retarded and appropriately grown fetuses, especially when the growth retardation was associated with pregnancy induced hypertension. Firstly, the growth- retarded fetuses showed a reduction in quantity of motor output, although an overlap existed with the normal fetuses. A quantitative reduction has also been reported by other investigators[7,16,17,18] mostly using non-imaging methods. Our study indicated a reduction in the number of movements as

well as a decrease in the duration of the individual general movements. The markedly reduced incidence of quick movements, such as startles, twitches and isolated arm movements, was striking, even in cases where the incidence of general movements was hardly reduced at all.

The qualitative analysis of general movements revealed a reduction in the quicker components in the growth-retarded fetus. There was a marked reduction of variability and fluctuation of speed and intensity within each general movement, leading to slow and monotonous movement patterns. There was high intra-individual consistency in the performance of the movement patterns. However, inter-individual differences existed, probably indicating varying degrees of functional impairment of the nervous system.

In infants and children, Touwen[20] has emphasized this intra-individual consistency of motor performances and referred to it as stereotypy of responses in cases of neurological abnormalities. Our results corroborate the findings in Prechtl and Nolte's study[13] on low and high risk preterm infants. Prechtl has furthermore drawn attention to the existence of qualitative changes of movement patterns in neurologically impaired infants.[13] These sick preterms later developed symptoms of severe neurological impairment. Abnormal motor behaviour was also found by Schulte et al.[19] in small for gestational age infants, born to mothers with pregnancy-induced hypertension. Neurological examination of these infants revealed low muscle power, weak reflexes and decreased general excitability. These neurological deficiencies could be expected to express themselves in deviant motor activity, such as observed in our cases.

Other indications that changes in the quality of motor patterns may occur in the fetus can be found in studies by Sadovsky[18] and Manning.[11] Sadovsky described that a relative increase in the number of "weak" movements, together with a decrease in "strong" movements, preceded a reduction in the number of movements. These changes in quality were recorded indirectly by maternal perception. Using real-time ultrasound, Manning devised a scoring system for the detection of the fetus at risk: the "biophysical profile".[11] One variable, "fetal tone", was asssessed by observing of the quality of a single limb movement. In normal fetuses, a rapid return to flexion was observed following extension of a limb, whereas in compromised fetuses this was not observed. The abnormal quality and reduced number of isolated arm movements and twitches found in our growth-retarded fetuses, confirm Manning's observations. However, one can dispute whether "low fetal tone" is the most appropriate description.

Differences in motor performance between growth-retarded and healthy fetuses may be attributable to several causes. Possible explanations include reduced muscle bulk, spatial restriction due to lack of amniotic fluid and

metabolic deprivation, with or without impairment of the nervous system. Reduced muscle bulk in the IUGR fetus might be responsible for the lack of power in the motor patterns of these infants, yet is unlikely to be responsible for the monotony and reduced variability of the movements. Likewise, spatial restriction might reduce the amplitude of the fetal movements, but is most unlikely to affect the other parameters. This has been confirmed in observations of a fetus in a pregnancy with prolonged rupture of the membranes. Despite the absence of amniotic fluid, the fetus moved normally with vigorous and powerful movements (D.J.Bekedam; unpublished observation). Metabolic deprivation, such as associated with hypoglycaemia and hypoxaemia, might be responsible for the type of abnormal patterns found in this study. It is known that acute hypoxaemia reduces fetal movements.[2] Yet, short-term metabolic disturbances alone are unlikely to be responsible for the consistent qualitative changes in fetal motility, for the same abnormal motor patterns were also seen several days after birth when the metabolic status had been restored and was adequate. This was found in a follow-up study, in which the motor behaviour of two of the growth-retarded infants was studied on the 5th day postnatally. Abnormal postnatal movement patterns have also been reported in the literature.[12 19] By exclusion, the hypothesis remains that the abnormal motor behaviour of the growth retarded fetus is due to impaired neural development, caused by chronic nutritional deprivation. The hypothesis is supported by several animal studies, indicating that severe intrauterine malnutrition can lead to reduced, defective neurocellular growth, myelinization or dendritic arborization.[1 6 7] The disturbed development of fetal behavioural states which has been reported in the IUGR fetus[21], illustrates that in the human also, chronic malnutrition may impair maturation of the central nervous system. The occurrence of reduced heart rate variability[22] and decreased breathing irregularity[5] in growth retarded-fetuses, increase the probability that the reduced variability of the general movement pattern may also be of central neural origin.

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References

1. Bedi KS. (1984): Effects of undernutrition on brain morphology: a critical review of methods and results. In: Current Topics in Research on Synapses. Alan R. Liss, Inc. Vol.2, 93-163.

2. Bekedam DJ, Visser GHA. (1985): Effects of "hypoxemic events" on breathing, body movements and heart rate variation. A study in growth-retarded human fetuses. Am. J. Obstet. Gynecol. 153:52.

3. Dickerson JWT. (1981): Nutrition, brain growth and development. In: Maturation and Development. Biological and Psychological Perspectives. Kevin J. Connolly and Heinz F.R. Prechtl.(Eds.) Clinics in Developmental Medicine no.77/78., William Heinemann Medical Books, London.

4. Dobbing J. (1981): The later development of the brain and its vulnerability. In: Scientific Foundations of Pediatrics. Davis,J.A. and Dobbing,J(Eds.). 2nd edition. Heinemann, London.

5. Dornan JC, Ritchie JWK, Ruff S. (1984) The rate and regularity of breathing movements in the normal and growth-retarded fetus. Br.J.Obstet.Gynaecol. 91:31-36.

6. Gruenwald P (1963): Chronic fetal distress and placental insufficiency. Biol. Neonate 5,215-265.

7. Jarvis GJ, MacDonald HN. (1979): Fetal movements in small-for-dates babies. Br.J. Obstet. Gynaecol. 86:724-727.

8. Jurgens-van der Zee AD, Biermann-van Eendenburg MEC, Fidler VJ, Olinga AA, Visch JH, Touwen BCL, Huisjes HJ. (1979): Preterm birth, growth retardation and acidemia in relation to neurological abnormality of the newborn. Early Human Develop. 3:141-154.

9. Kloosterman GJ. (1970): On intrauterine growth. The significance of prenatal care. Int.J. of Gynaecol. Obstet. 8:895-912.

10. Leyon I, Finnstrom O, Nilsson B. (1980): Neurology of growth-retarded neonates. Relation to biochemical placental function tests in late pregnancy. Early Human Develop. 4:257-270.

11. Manning FA, Platt LD, Sipos L. (1979): Antepartum fetal evaluation: Development of a fetal biophysical profile. Am.J.Obstet.Gynaecol. 136:787-791.

12. Michaelis R, Schulte FJ, Nolte R. (1971): Motor behaviour of the small-for-gestational age newborn infants. J. Pediatr. 76:208-213.

13. Prechtl HFR, Nolte R.(1984): Motor-behaviour of preterm infants. In: Continuity of neural functions from prenatal to postnatal life. Ed. H.F.R. Prechtl. Blackwell Scientific Publications Ltd., Oxford, England, Clinics in Developmental Medicine, no. 94, 79-92.

14. Prechtl HFR, Fargel JW, Weinmann HM, Bakker HH.(1979): Posture, motility and respiration in low-risk pre-term infants. Develop.Med. Child Neurol. 21: 3-27.

15. Prechtl HFR.(1977): The neurological examination of the full-term newborn infant. In: Clinics in Developmental Medicine, no. 63, 2nd edn, Heinemann Medical Books Ltd,London.

16. Roberts AB, Little D, Cooper D, Campbell S. (1978): Fetal activity in normal and abnormal pregnancies. Proc. 5th Fetal Breathing conference, Nijmegen, Ed. T.K.A.B. Eskes, University Press, Nijmegen, The Netherlands.

17. Sadovsky E, Yaffe H. (1973): Daily fetal movement recording and fetal prognosis. Obstet. Gynecol. 41:845-849.

18. Sadovsky E, Laufer N, Allen JW. (1979): The incidence of different types of fetal movements during pregnancy. Br.J.Obstet.Gynaecol. 86:10-14.

19. Schulte FJ, Schrempf G, Hinze G. (1971): Maternal toxemia, fetal malnutrition and motor behaviour of the newborn. Ped. 48:871-882.

20. Touwen BCL. (1978): Variability and stereotypy in normal and deviant development. Clinics in Developmental Medicine, Heinemann, London, 67:99-110.

21. Vliet van MAT, Martin Jr. CB, Nijhuis JG, Prechtl HFR. (1985): Behavioural states in growth retarded human fetuses. Early Human Develop. 12:183-197.

22. Visser GHA. (1984): Antenatal cardiotocography in the evaluation of fetal well-being. Austr.NZ.J. Obstet Gynaecol. 24:80-85.

23. Vries de JIP, Visser GHA, Prechtl HFR. (1982): The emergence of fetal behaviour. I.Qualitative aspects. Early Human Develop. 7: 301-322.

24. Vries de JIP, Visser GHA, Prechtl HFR. (1985): The emergence of fetal behaviour. II Quantitative aspects. Early Human Develop. 12:99-120.

7

ABNORMAL UMBILICAL ARTERY WAVEFORM PATTERNS IN GROWTH-RETARDED FETUSES: RELATIONSHIP TO ANTEPARTUM LATE HEART RATE DECELERATIONS AND OUTCOME

Summary

In 70 intrauterine growth-retarded (IUGR) fetuses with antepartum late heart rate decelerations umbilical artery velocity waveform recordings were made with Doppler ultrasound and calculated as pulsatility indexes (PI). In 29 of these fetuses longitudinal recordings were made. Abnormal PIs preceded the occurrence of late heart rate decelerations in 27 (93%) of the 29 fetuses. The median duration of the interval between the first abnormal PI and the first appearance of late heart rate decelerations was 17 days (range 0 - 60 days). This wide range can mainly be attributed to the gestational age at which the first abnormal velocity waveform was recorded; during early gestation the interval was much longer, than later in pregnancy. Absent end-diastolic velocity (AEDV) was found in 15 of the 29 fetuses (59%) and preceded the occurrence of decelerations with a median interval of 12 days (range 0-49 days).

In the total group, 4 of the 70 IUGR fetuses with antepartum decelerations had a normal umbilical artery velocity waveform pattern. Fetuses with AEDV (n=45) were more severely growth retarded and were delivered at an earlier gestational age than those with end-diastolic velocity (n=25). Also perinatal mortality and morbidity were higher in the group with AEDV. Yet, when fetuses were matched for gestational age and birth weight no differences in perinatal outcome were found between those with and those without end-diastolic velocity.

Introduction

In intrauterine growth-retarded (IUGR) fetuses abnormal umbilical artery blood velocity waveform patterns identify fetuses at risk for developing perinatal distress. [1 2 3] In general, changes in Doppler waveforms tend to precede antepartum fetal heart rate (FHR) abnormalities. [1 2 4 5] The latter are

reliable, but rather late signs of fetal compromise and are associated with hypoxaemia and sometimes acidaemia at birth. [6789]

In a group of severely growth-retarded fetuses, we studied the relationship between Doppler velocity waveform patterns of the umbilical artery and the occurrence of antepartum late heart rate decelerations, to investigate: 1) whether abnormal waveforms always precede the occurrence of late heart rate decelerations, 2) the time interval between abnormal waveform patterns and the development of heart rate decelerations, 3) whether absent end-diastolic velocity (AEDV) always forms an indication for immediate delivery or whether pregnancy might be continued for some time, 4) differences in perinatal outcome between fetuses with and without end-diastolic velocity.

Patients and methods

The study group was selected retrospectively and consisted of all women admitted to our department for intrauterine growth retardation in the period January 1986 to July 1988, in whom antepartum late heart rate decelerations developed in the fetus. Further criteria for selection were, delivery by elective Caesarean section (CS), birth weight below the 10th centile corrected for sex, parity and gestational age (10) and no congenital malformations. All pregnancies were well dated. The study group consisted of 70 women. Their clinical data are shown in Table 1.

Fetal heart rate monitoring was performed daily for at least 45 minutes (Hewlett Packerd 8040A). The timing of delivery was based on the cardiotocographic findings, taking into account gestational age, growth assessment, obstetrical history and other complications during pregnancy. Doppler recordings were performed at weekly intervals using a 4 mHz continuous Doppler device (Doptek). A high pass filter of 150 Hz was used, which means that no frequency shifts could be detected below this level. The pulsatility index (PI) was calculated as the peak systolic velocity minus the peak diastolic velocity divided by the mean velocity. This calculation was made over 5 cardiac cycles in the absence of fetal breathing and body movements. The final PI value from a weekly examination was taken as the average of the PIs over 3 recordings of 5 cardiac cycles. Absent end-diastolic velocity (AEDV) was noted if no diastolic frequencies were detected in all 3 recordings. The Doppler velocity waveforms were related to a reference curve made at our department. The results of the Doppler recordings were not withheld from the clinicians.

Table 1
Clinical data of the patients (n=70), presented according to the umbilical artery velocity waveform pattern directly before delivery.

	Umbilical artery velocity waveform		
	Normal	Abnormal	
		EDV	AEDV
	n=4	n=21	n=45
Mean age (in years)	34	31	30
Parity - nulliparae (n)	0	7	26
- multiparae (n)	4	14	19
PIH (n)	4	16	31
Albuminuria (n)	4	4	14
Antihypertensive drugs (n)	2	5	8
Diabetes mellitus (n)	0	0	3

AEDV = absent end-diastolic velocity
EDV = end-diastolic velocity
PIH = pregnancy induced hypertension

In all 70 subjects the last recording of the umbilical artery PI was made within 72 hours of CS. The results of these recordings will be presented as "cross-sectional data". Subjects who were followed for more than one week and had a normal initial FHR trace, were included into the "longitudinal study" (n=29).

Neonatal outcome was asssessed according to birth weight and percentile, Apgar Score, umbilical cord gases, perinatal mortality and neonatal complications. The reference values for cord blood gases and pH at elective CS have been published previously. [7]

Results

1. Longitudinal study (n=29);

In the 29 subjects with normal initial FHR traces, whose fetuses developed antepartum late decelerations during admission, a median number of 6 Doppler measurements of the umbilical artery were made (range 3-18). The median interval between the first recording and CS was 42 days (range 12-140 days).

At the onset of decelerations, 2 (7%) had a normal PI, 10 had an increased PI with end-diastolic velocity (34%) and 15 had AEDV (59%). The median gestational age at which decelerations occurred was slightly lower in cases with AEDV than those with end-diastolic velocity (32.4 and 34.4 weeks, respectively; Mann-Withney U test, $p<0.05$).

Of the 29 cases, 19 had a normal PI at the first recording. Figure 1 shows the change in PI occurring with time in these patients. The median interval between the first abnormal PI and the onset of late heart rate decelerations was 17 days (range 0-60 days). When plotted according to the gestational age at which the first abnormal PI was recorded, it appeared that the interval between first abnormal PI and the occurrence of decelerations was much longer during early gestation than in later pregnancy ($r=-0.8$, $p<0.002$, Fig. 2).

There were 10 cases in whom the PI changed from a pattern with end-diastolic velocity to AEDV. The interval between the occurrence of AEDV and the first deceleration had a range of 0 to 49 days, i.e. one case had AEDV for 7 weeks before decelerations occurred. Including the five cases who were admitted with AEDV, the median interval between AEDV and the occurrence of late FHR decelerations was 12 days.

The median interval between the first appearance of late heart rate decelerations and delivery was 2 days (range 0-23 days). The overall median interval between the first abnormal PI value of the umbilical artery and CS was 21 days (range 0-70 days).

2. Cross-sectional study (n=70)

Within 72 hours of delivery, 4 of the 70 fetuses (6%) had a normal PI of the umbilical artery, 21 had an increased PI with end-diastolic velocity (30%) and 45 had AEDV (64%) (Figure 3).

The outcome of the 3 groups is shown in Tables 2 and 3. The infants with AEDV had a lower one-minute Apgar score and a lower pH and pO_2 in the umbilical artery and vein than those with end-diastolic velocity. However, these differences were not statistically significant. The AEDV infants were also born at an earlier gestational age, were more growth retarded than the

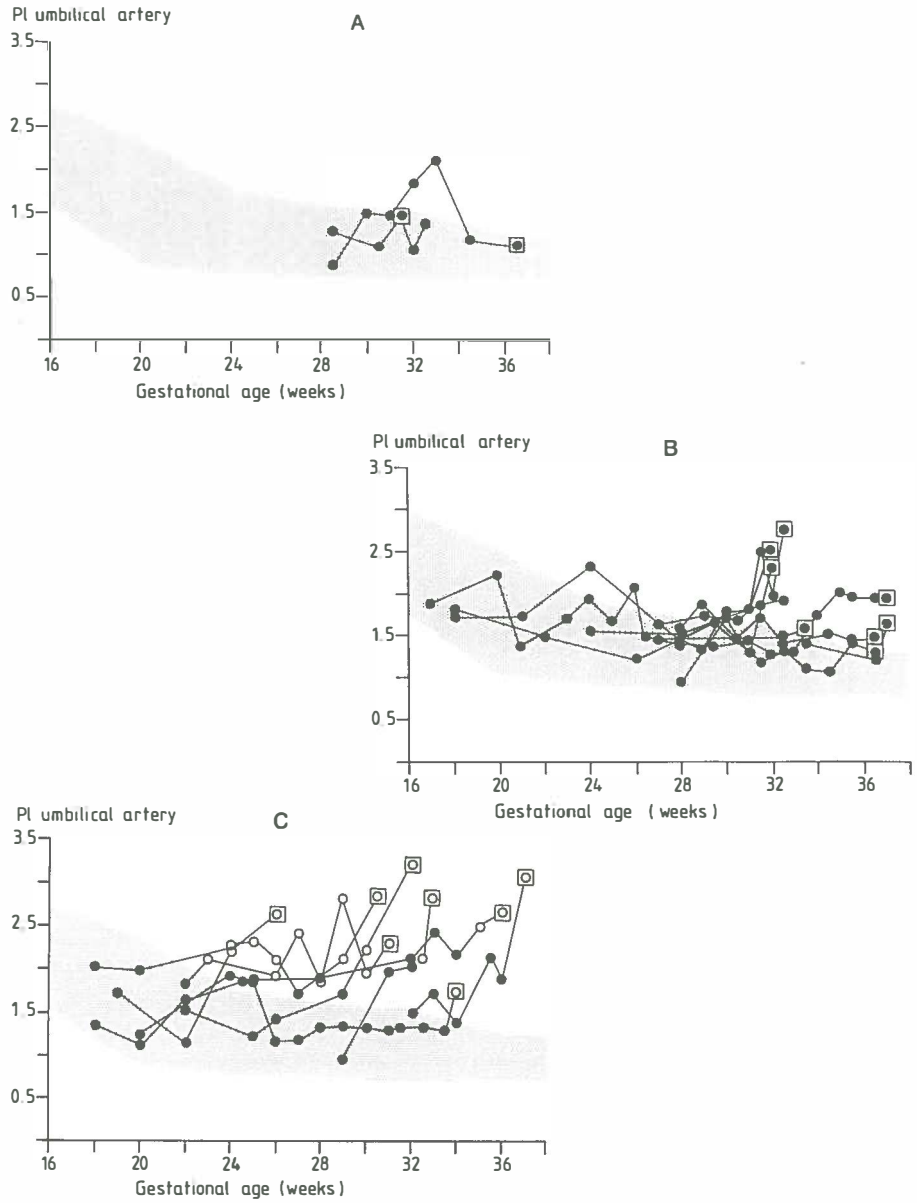

Fig. 1

Pulsatility index (PI) of the umbilical artery in 19 IUGR fetuses who initially had normal PI values and who developed late heart rate decelerations (□= first occurrence of deceleration).

A) 2 fetuses with a normal PI when decelerations occurred; B) 9 fetuses with an abnormal PI but with end-diastolic velocity; C) 8 fetuses who developed decelerations with AEDV (open symbols indicate AEDV).

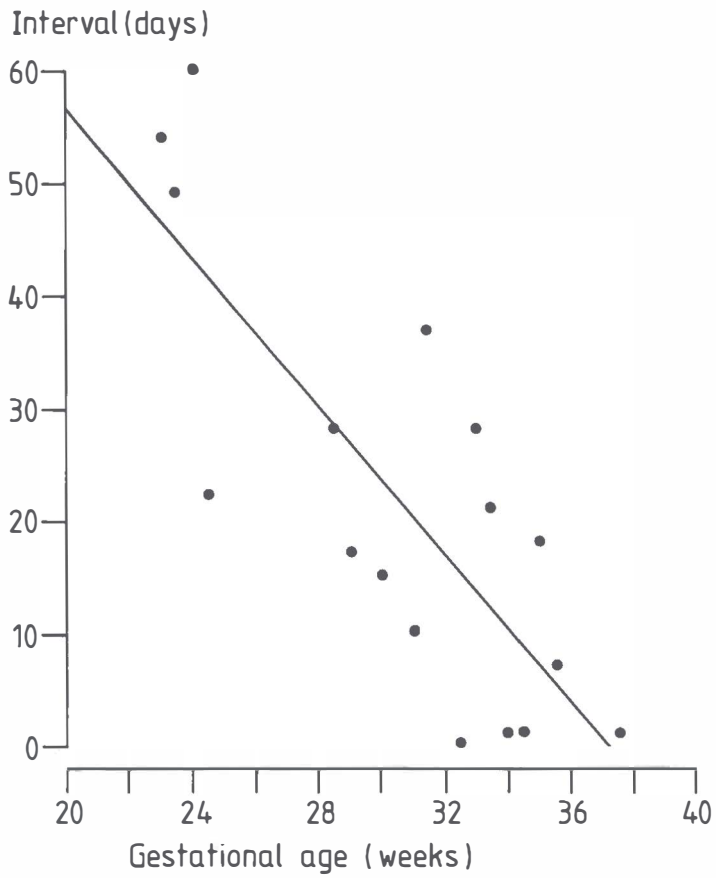

Fig. 2
Interval between the first abnormal blood velocity waveform pattern and the occurrence of late heart rate decelerations in 17 fetuses who were followed longitudinally. Data are plotted according to gestational age at which the first abnormal waveform pattern was found (Linear correlation r=-0.8, n=17, $p < 0.002$).

infants in the other groups and had higher neonatal morbidity and mortality rates. To investigate the effect of the PI variable on outcome, we were able to match 13 cases with and 13 cases without end-diastolic velocity for gestational age and birth weight (Table 4). There were no significant differences between the two groups. This indicates that other variables, such as gestational age at delivery and birth weight are much more important than the actual PI.

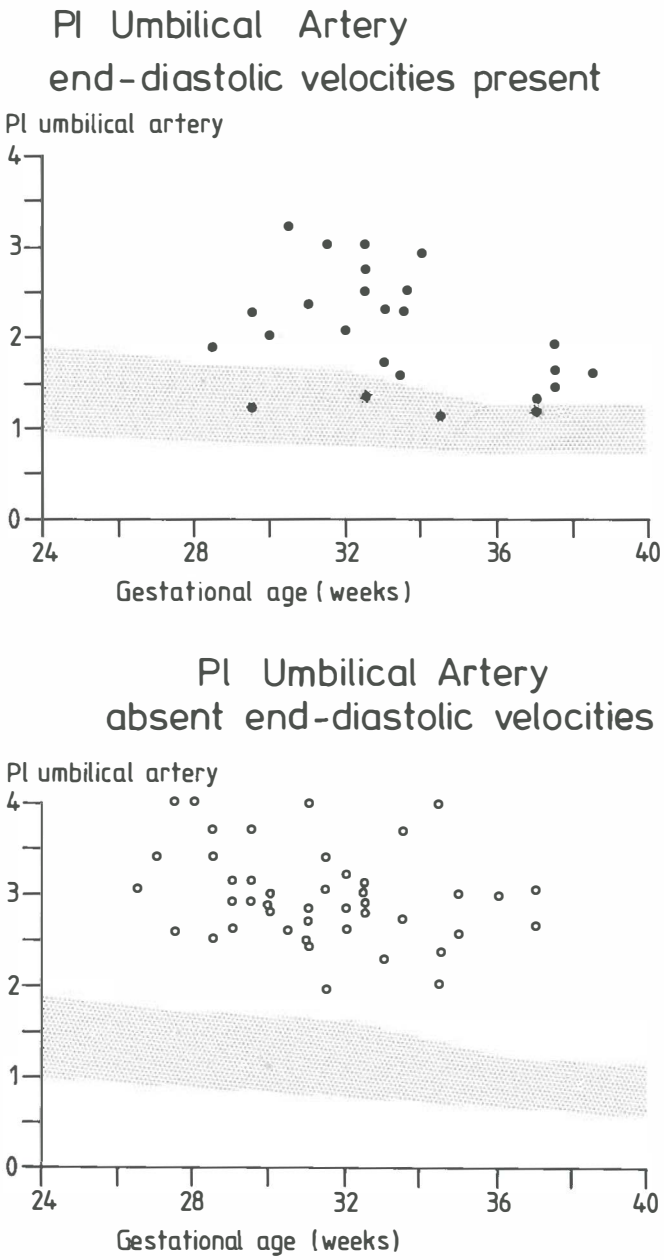

Fig. 3
PI value of the umbilical artery within 72h of CS of 70 IUGR fetuses with late heart rate decelerations. a) 25 fetuses with present end-diastolic velocity; b) 45 fetuses with absent end-diastolic velocity.

Table 2
Fetal and neonatal outcome of IUGR fetuses with late heart rate decelerations according to the umbilical artery velocity waveform pattern.

	Umbilical artery velocity waveform pattern		
	Normal	Abnormal	
		EDV	AEDV
	n=4	n=21	n=45
Gestational age at delivery (weeks): (mean + range)	33.3 29.5-37	33.2 28.5-38.3	31.1 26.3-37.2
Birth weight (g) (mean + range)	1490 (920-2180)	1365 (885-2410)	991 (450-2210)
Birth weight centile (n)			
< 2.3	0	4	29
2.3-5.0	1	5	4
5.0-10.0	3	12	12
Apgar score (mean +sem)			
1 min:	5.3(+3.1)	5.8(+0.6)	4.3(+0.4)
5 min:	6.7(+2.0)	8.2(+0.4)	7.6(+0.3)
Intrauterine death (n)	0	1	2
Neonatal death (n)	0	2	11
Intubation* (n)			
< 1 day :	1	4	5
1-7 days :	1	3	6
> 7 days :	0	0	8
Intraventricular haemorrhage* (n)	0	1	8
Necrotising enterocolitis (n)	0	1	2

* including neonatal deaths
EDV = end-diastolic velocity
AEDV = absent end-diastiolic velocity

Table 3
Blood gas values from umbilical artery and vein at elective Caesarean section (CS) of the IUGR fetuses with normal and abnormal Doppler waveform patterns and of a control group of non-compromised fetuses (see ref 7).

	IUGR			Control
	Umbilical artery velocity waveform pattern			
	Normal	Abnormal		
		EDV	AEDV	
	(n=4)	(n=21)	(n=45)	(n=45)
Umbilical Artery: (mean + sem)				
-pH	7.15 (0.04)	7.24 (0.01)	7.19 (0.02)#	7.25 (0.01)
-pO_2 (kPa)	2.02 (0.78)	1.96 (0.19)*	1.77 (0.13)#	2.81 (0.11)
-pCO_2 (kPa)	9.59 (0.75)	7.74 (0.16)*	8.01 (0.42)#	7.30 (0.19)
-Base excess	8.33 (2.19)	5.49 (0.86)	7.51 (0.80)	4.89 (0.50)
Umbilical Vein: (mean + sem)				
-pH	7.25 (0.03)	7.27 (0.01)	7.26 (0.01)#	7.31 (0.01)
-pO_2 (kPa)	3.70 (0.62)	3.47 (0.24)*	3.23 (0.17)#	4.66 (0.16)
-pCO_2 (kPa)	9.59 (0.75)	6.47 (0.16)*	6.97 (0.26)#	5.92 (0.13)
-Base excess	9.30 (1.92)	6.58 (0.84)	6.09 (0.70)#	4.01 (0.30)

EDV = end-diastolic velocity
AEDV = absent end-diastolic velocity

* Control group versus IUGR with end-diastolic velocity ($p < 0.05$ to $p < 0.005$, Mann-Withney U-Test).
\# Control group versus IUGR with AEDV ($p < 0.05$ to $p < 0.005$, Mann-Withney U-Test).

At delivery the 4 cases with a normal PI showed the same degree of abnormality in the blood gas values as those with an abnormal PI, indicating a similar degree of fetal compromise (Table 3).

In 5 fetuses, reversed end-diastolic velocity was found in the last Doppler examination. As reversed flow was not present in all 3 recordings, these fetuses are not presented as a separate group but have been included in the group with AEDV. The perinatal outcome was, poor however, as only 2 of the 5 infants survived.

Table 4
Fetal and neonatal outcome in 13 fetuses with end-diastolic velocity compared to that of 13 with absent end-diastolic velocity in the umbilical artery. The groups are matched for gestational age and birth weight.

	Umbilical artery velocity waveforms end-diastolic velocity		
	present	absent	
Gestational age in wks. (mean + range)	31.9 (29.5-37.5)	31.9 (29.2-37.2)	
Birth weight (g) (mean + range)	1146 (885-1735)	1138 (780-1620)	
Blood gas values (mean +SD)			
Umbilical artery:			
-pH	7.23 (+0.04)	7.18 (+0.04)	ns
-pO_2 (kPa)	1.78 (+0.6)	1.89 (+0.7)	ns
-pCO_2 (kPa)	7.84 (+0.9)	8.05 (+3.1)	ns
Umbilical vein:			
-pH	7.28 (+0.04)	7.24 (+0.08)	ns
-pO_2 (kPa)	3.26 (+0.6)	3.34 (+0.8)	ns
-pCO_2 (kPa)	6.65 (+0.8)	6.75 (+2.0)	ns
Apgar scores (mean +SD)			
- 1 min	5.2 (+2.6)	4.1 (+2.3)	ns
- 5 min	7.8 (+1.8)	7.6 (+1.8)	ns
Perinatal mortality (n)	1	1	
Intubation (n)	5	3	
Intraventricular haemorrhage (n)	0	2	
Necrotising enterocolitis (n)	1	1	

Mann-Whitney U Test; ns= not significant.

Discussion

This study confirms that IUGR fetuses with antepartum late heart rate decelerations are generally hypoxaemic and (mildly) acidaemic. This has been shown before in cord blood obtained at elective CS [7 8] and by blood samples taken by cordocentesis. [9] In the absence of decelerations, blood gases in IUGR fetuses are usually within the (lower) normal range. [7 9] The occurrence of antepartum decelerations is, therefore, a good marker of impaired fetal oxygenation.

Some authors have reported that abnormal umbilical artery velocity waveform patterns precede abnormal FHR patterns in IUGR fetuses. [1 2 4 5] Our results are in agreement, but occasionally decelerations may occur with normal umbilical artery velocity waveform patterns (6%). The blood gases at birth of the 4 cases with a normal PI revealed a true fetal impairment. This indicates that a normal umbilical artery PI cannot be considered as definite proof of fetal well-being.

There was a large range of intervals between the first abnormal PI and the onset of decelerations (0-60 days median 17 days). This could partly be attributed to differences in gestational age. During early gestation, the time-interval between the first occurrence of an abnormal PI and the onset of decelerations was much longer than in later pregnancy. This might be explained by a decline in placental reserve capacity during the course of pregnancy; the smaller the fetus, the lower are its nutritional and oxygen requirements and the longer it might remain in a reasonable condition. Another explanation might be that during early gestation fetuses, are less sensitive to changes in oxygenation (due to differences in chemoreceptor setting?) and are only liable to develop decelerations at a late stage of impairment. The latter is unlikely, however, as at least from 27 weeks onwards, fetuses tend to develop decelerations when the pO_2 falls below two standard deviations of the norm, irrespective of the duration of pregnancy. [9]

The fact that Doppler velocity waveform abnormalities generally precede the occurrence of antepartum FHR decelerations, suggests that they are already abnormal while the fetal pO_2 is still within the (lower) normal range. It is, therefore, unlikely that Doppler measurements will give a precise indication of the actual degree of impairment. Cordocentesis data have shown that even with severely abnormal waveform patterns (AEDV), the fetal pO_2 and the pH are still within the normal range in 20% and 60% of the cases, respectively. [11]

The present study indicates that with late decelerations fetal outcome is poorer in cases with AEDV than in those with end-diastolic velocity in the umbilical artery. This has also been shown in IUGR fetuses with AEDV in the fetal aorta and it has been suggested that IUGR fetuses should be delivered before these severe waveform abnormalities occur. [12] However, in the study by Hackett et al. [12] and in the present one, fetal growth retardation was generally more severe in fetuses with AEDV. They were also delivered at an earlier age than fetuses with end-diastolic velocity. When we matched for age and birth weight no clear differences in outcome between fetuses with and without end-diastolic velocity were found. This indicates that AEDV in the umbilical artery is more a marker of early and severe IUGR - which by itself has an effect on outcome - than a marker purely related to outcome. Delivery at an earlier gestational age might lead to an even higher neonatal morbidity rate. The more so, because during early gestation the prognosis of IUGR infants is mainly determined by the gestational age at birth. [13]

There were 5 cases with AEDV for more than 3 weeks. These infants were delivered between 30 and 35 weeks of gestation. There was one neonatal death, but all the others did well after birth. This was also valid for the infant delivered at 31 weeks who had had AEDV for more than 7 weeks (birth weight 900 g). These data stress that at early gestation, AEDV is not necessarily an indication for direct delivery and that important weeks of maturation may be gained.

Reversed end-diastolic velocity, however, may form an indication for aggressive perinatal management as has been advised recently. [14] The perinatal outcome in the present study was also poor, as only 2 of these 5 infants survived. Data on this phenomenon are still limited and should be interpreted with caution. In the interpretation of the present data it has to be emphasized that our IUGR fetuses were selected on the presence of late heart rate decelerations, so therefore we cannot comment on the prevalence and predictive value of abnormal umbilical artery velocity waveforms in growth retardation in general.

In conclusion, in IUGR fetuses abnormal umbilical artery verlocity waveform patterns generally precede the occurrence of antepartum decelerations by several weeks. However the duration of this time interval differs considerably between fetuses and occasionally decelerations occur when Doppler recordings are still normal. This indicates that a normal umbilical artery PI cannot be considered as definitive proof of fetal well-being and that Doppler recordings are of limited value as to the timing of delivery. But abnormal Doppler recordings do form a strict indication for intensive fetal heart rate monitoring.

References

1. Reuwer PJHM, Rietman GW, Sijmons EA, van Tiel MWM, Bruinse HW. (1987): Intrauterine growth retardation: prediction of perinatal distress by doppler ultrasound. Lancet, i:415-418.

2. Trudinger BJ, Cook CM, Jones L, Giles WB. (1986): A comparison of fetal heart rate monitoring and umbilical artery waveforms in the recognition of fetal compromise. Br. J. Obstet. Gynecol., 93:171-175.

3. Laurin J, Marsal K, Persson P, Lingman G. (1987): Ultrasound measurement of fetal blood flow in predicting fetal outcome. Br. J. Obstet. Gynecol. 94:940-948.

4. Arabin B, Siebert M, Jimenez E, Saling E. (1988): Obstetrical characteristics of the loss of end-diastolic velocities in the fetal aorta and/or umbilical artery using doppler ultrasound. Gynaecol. Obstet. Invest. 25:173-180.

5. Rochelson B, Schulman H, Farmakides G, Bracero L, Ducey J, Fleischer A, Penny B, Winter D. (1987): The significance of absent end-diastolic velocity in umbilical artery velocity waveforms. Am. J. Obstet. Gynecol. 156:1213-1218.

6. Visser GHA, Redman CWG, Huisjes HJ, Turnbull AC. (1980): Non-stressed antepartum heart rate monitoring: implications of decelerations after spontaneous contractions. Am. J. Obstet. Gynecol. 138:429-435.

7. Bekedam DJ, Visser GHA, Mulder EJH, Poelmann-Weesjes G. (1987): Heart rate variation and movement incidence in the growth-retarded fetuses: the significance of antenatal late heart rate decelerations. Am. J. Obstet. Gynecol. 157:126-133.

8. Smith JH, Anand KJS, Cotes PM, Dawes GS, Harkness RA, Howlett TA, Rees LH, Redman CWG. (1988): Antenatal fetal heart rate variation in relation to the respiratory and metabolic status of the compromised human fetus. Br. J. Obstet. Gynaecol. 95:980-989.

9. Visser GHA, Sadovsky G, Nicolaides KH. (1989): Antepartum heart rate patterns in small-for-gestational age third trimester fetuses: correlations with blood gases obtained at cordocentesis. Am. J. Obstet. Gynecol. in press.

10. Kloosterman GJ. (1970): On intrauterine growth. The significance of prenatal care. Int. J. Gynecol. Obstet. 8:895-912

11. Nicolaides KH, Bilardo CM, Soothill PW, Campbell S. (1988): Absence of end diastolic frequencies in umbilical artery: a sign of fetal hypoxia and acidosis Br. Med. J. 297:1026-1027.

12. Hackett GA, Nicolaides KH, Campbell S. (1987): Doppler studies in the growth-retarded fetus and the prediction of necrotising enterocolitis, haemorrhage and neonatal morbidity. Br. Med. J. 294:13-16.

13. Yu VYH, Loke HL, Bajuk B, Szymonowicz W, Orgill AA, Astbury J. (1986): Prognosis for infants born at 23 to 28 weeks' gestation. Br. Med. J. 293:1200-1203.

14. Brar HS, Platt LD. (1988): Reverse end-diastolic flow velocity on umbilical artery velocimetry in high-risk pregnancies: An ominous finding with adverse pregnancy outcome. Am. J. Obstet. Gynecol. 159:559-561.

8

General discussion and summary

Changes in fetal behaviour and the cardiovascular system with progressive deterioration of the fetal condition in growth retardation

Introduction

In this chapter a possible rank order is presented of changes in fetal heart rate patterns, body movements and Doppler waveform patterns of the umbilical artery, which occur with progressive deterioration of the fetal condition. The rank order is derived from the studies of this thesis and from recent literature. It might be of help to the clinician when determining the timing of delivery of the growth-retarded fetus and for increasing our understanding of the diagnostic value of the various assessment techniques. The changes in fetal behaviour and in the cardiovascular system are related to fetal and neonatal blood gas values and are discussed in the light of neonatal neurological morbidity.

This thesis focuses on intrauterine growth retardation, caused by reduced nutrient and oxygen supply to the fetus and placenta, due to impaired uteroplacental perfusion. This metabolic shortage leads to a more or less progressive deterioration in the fetal condition. It must be kept in mind that the endpoint of this chronic process may vary considerably, from a slightly dystrophic term newborn to fetal death in utero. This depends on the severity of uteroplacental impairment and on the ability of the fetus to compensate for the reduction in metabolic supply. The suggested rank order is based on the assumption that the process of deterioration is a continuum.

Heart rate variation and heart rate decelerations in IUGR fetuses

Murata et al. (1982) found that with progressive deterioration of the fetal condition in the rhesus monkey, late heart rate decelerations appeared first. This condition was associated with fetal hypoxaemia (Table 1). The number

of accelerations (and movements?) decreased later, when the arterial pH also fell. [23] This indicates that fetuses with suboptimal oxygenation may exhibit late decelerations with uterine contractions, even though other blood gas and biophysical variables are normal. In growth retarded fetal sheep, Robinson et al. (1985) have reported that chronic hypoxaemia (and hypoglycaemia) can be present for weeks before acidaemia and finally intrauterine death occurs. [32] Other animal experiments, in which the mechanisms of late heart rate decelerations were studied, confirm the importance of the status of fetal oxygenation. [16 24]

The aetiology of late heart rate decelerations is still open for debate and especially the role of the baroreceptors is disputed. As in animal experiments, late decelerations are not uniformly accompanied by fetal hypertension, they are mainly thought to be a chemoreceptor response to hypoxaemia. Thus, one mechanism of generation of late heart rate decelerations is chemoreceptor-activated vagal activity, mediated via cardio-inhibitory centres. A second mechanism must also play a role, as decelerations are sometimes only slightly modified by parasympathetic blockade by atropine. [3] As myocardial oxygen consumption is reduced it has been concluded that late decelerations also partly result from hypoxic myocardial depression. [3 7 19]

Table 1
Fetal arterial blood gas and pH values (mean and range) found with progressive deterioration of the fetal condition in the rhesus monkey (Murata et al, 1982) [23]

	At beginning of observation	At appearance of late deceleration	Disappearance of acceleration
pH	7.37 (7.31-7.43)	7.32 (7.20-7.37)	7.22* (7.20-7.25)
pO_2 (mm Hg)	27.6 (23.0-31.8)	23.9† (21.8-27.5)	18.7# (15.0-25.4)
pCO_2 (mm Hg)	29.8 (26.6-32.0)	33.9 (28.2-40.5)	38.8 (26.0-49.5)

*p = 0.002 versus control; p = 0.048 versus appearance of late deceleration.
†p = 0.041 versus control; p = 0.021 versus disappearance of acceleration.
#p = 0.009 versus control; p = 0.021 versus appearance of late deceleration.

Heart rate variability during the deceleration is thought to be a measure of the degree of hypoxic myocardial depression. Where the latter mechanism predominates over the increased vagal and ß-adrenergic activity, heart rate variability is reduced or absent. [7]

There is evidence that changes in heart rate (and movement) patterns in the growth-retarded human fetus more or less follow the same pattern as found in the rhesus monkey. A possible rank order in which these changes occur with progressive deterioration of the fetal condition is shown in Fig. 1. Centrally placed in this figure, is the occurrence of late heart rate decelerations. In Chapter 3, two sub-groups of growth-retarded fetuses were studied: 29 fetuses with antenatal heart rate decelerations were compared to 8 growth retarded fetuses without decelerations. At primary (elective) Caesarean section significantly lower pO_2 values were found in the decelerative group in both the umbilical artery and vein. No differences were found in pH values, indicating that in growth-retarded fetuses antenatal heart rate decelerations are associated with fetal hypoxaemia and not with acidaemia (Chapter 3). Recently this has been confirmed by comparing antepartum heart rate records to fetal blood gases, obtained at cordocentesis. In 41 out of the 45 small-for-gestational age fetuses with a normal ("reactive") heart rate pattern,

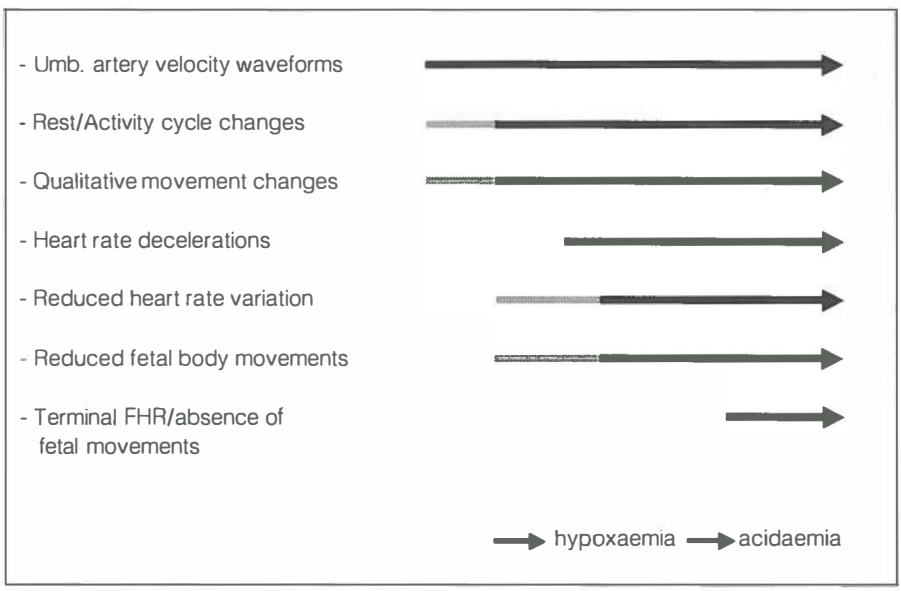

Fig. 1
Suggested rank order of changes in heart rate and behavioural patterns, which occur with progressive deterioration of the growth-retarded fetus.

pO_2 values were normal, whereas acidaemia was absent in all 45 cases. In the presence of late decelerations, however, 12 out of the 13 fetuses were hypoxaemic and/or mildy acidaemic. [48] These studies permit the conclusion that the occurrence of late heart rate decelerations is a good marker of fetal compromise.

Using a computerized numerical analysis, it has been shown that in IUGR fetuses in the absence of decelerations, heart rate variation is within the (lower) normal range. [44] Only after late heart rate decelerations have been recorded do baseline heart rate variation and the incidence of accelerations fall below the normal range in the majority of cases (88%) (Chapter 3). This implies that, in general, heart rate variation in growth-retarded fetuses cannot be distinguished from that of appropriately grown fetuses before late decelerations occur and consequently, that reduced heart rate variation has to be considered a rather late sign of fetal compromise.

It has been shown that long-term heart rate variation is reduced before fetal acidaemia has developed [15] (Chapter 3). The initial reduction in heart rate variation is, therefore, not caused by fetal acidaemia. Hypoxaemia, on the other hand may play a role, because IUGR fetuses with the lowest heart rate variation had significantly lower pO_2 values than fetuses with higher heart rate variation, whereas no differences in pH were found (Chapter 3). After reviewing the data of Chapter 3, a significant correlation between baseline heart rate variation ("RMS") and umbilical artery pO_2 values was also

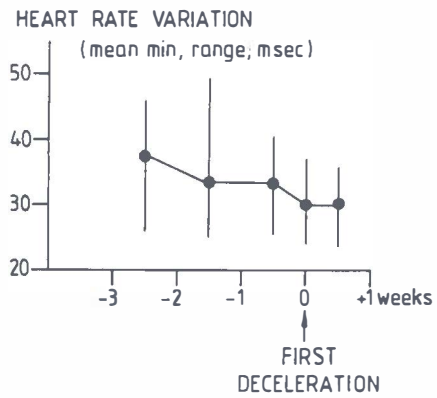

Fig. 2
Overall heart rate variation, expressed as mean minute range, of growth-retarded fetuses studied longitudinally. On average heart rate variation fell below the norm (30 msec) at the same time decelerations occurred. (reproduced with permission from Snijders et al., 1989)

found (r=0.42 p<0.002). Smith et al. (1988) reported a similar correlation between overall heart rate variation (expressed as "mean minute range") and umbilical artery pO_2 (r=0.52). [39] These data indicate that the decrease of heart rate variation coincides with the occurrence of (chronic) fetal hypoxaemia, just as the presence of heart rate decelerations. These changes - the appearance of heart rate decelerations and of decreased variation - seem to occur at the same time in the process of deterioration of the fetal condition. Recently this has been confirmed in a longitudinal study on 13 growth-retarded fetuses in whom heart rate records were analysed using an on-line computer system. [40] There was a gradual fall in overall heart rate variation with time and, on average, variation fell below the norm (=30msec) at the same time as heart rate decelerations occurred (Fig. 2). However, interfetal

Table 2
Heart rate records 3 to 12 days before intrauterine death analysed visually by means of the Fischer score. (Adapted from J.W. v.d. Slikke 1981). [38]
Late heart rate decelerations occurred at the same time as the reduction in oscillatory amplitude and reduction in accelerations.

	Days before intrauterine death		
	12 days (n=6)	5-6 days (n=9)	1-0 days (n=11)
late decelerations			
absent	4	3	0
present	2	6	11
oscillatory amplitude			
10-30 Bpm (2)	2	0	0
5-9 Bpm (1)	4	7	3
1-5 Bpm (0)	0	2	8
oscillatory frequency			
> 6 n/min	6	6	0
2-6 n/min	0	2	7
< 2 n/min	0	1	4
accelerations			
sporadic (2)	4	5	0
periodic (1)	0	1	0
none (0)	2	3	11
heart rate			
120-160 Bpm	6	9	11

differences were present: in some fetuses reduced variation preceded the occurrence of decelerations by weeks, whereas in others variation fell only after the occurrence of decelerations. Although the presence of late heart rate decelerations is a good marker of fetal compromise, the absence of decelerations in one or more recordings does not, therefore, exclude fetal impairment. The absence of decelerations in some cases with reduced heart rate variation might be due to the limited recording time (1 hour per day). Data on the prevalence of heart rate decelerations in prolonged recordings in growth retarded fetuses are not yet available, nor is there information on possible diurnal variations in the occurrence of decelerations.

In small-for-gestational age fetuses, the different components of the fetal heart rate pattern (accelerations, baseline variation, decelerations) have been related to blood gases obtained at cordocentesis. [48] All three variables, mentioned above, had almost the same positive and negative predictive values for fetal hypoxaemia and/or acidaemia. This also suggests that with progressive deterioration of the fetal condition, changes in these components occur approximately at the same time. More or less similar findings were made by Van Der Slikke (1981). He analysed fetal heart rate patterns, using the Fischer score, in 13 growth-retarded fetuses 3 to 12 days before intrauterine death. [38] As can be seen from Table 2 heart rate decelerations occurred at the same time band width decreased and accelerations disappeared. This indicates, that these variables change from normal to abnormal at about the same time in the course of fetal deterioration.

The temporary decrease in heart rate variation directly after "hypoxaemic" events (late decelerations) as described in chapter 4 and the increase during maternal hyperoxygenation (Chapter 5) further confirm the relationship between heart rate variability and the oxygenation status of the fetus. [51] The mechanisms underlying the decrease and increase in heart rate variation after changes in fetal oxygenation are unknown. Yet, as fetal body and breathing movements change concomitantly, a change in the fetal brain activity state is a possible explanation. Changes in fetal behavioural states after prolonged uterine contractions associated with decelerations (i.e. hypoxaemia) have been reported in the human fetus. [45] Furthermore, the modulation of behavioural state by induced hypoxaemia in fetal sheep also fits into this picture. [14 20]

With a decelerative cardiotocogram, as shown in Fig. 3, decelerations have a variable pattern and do not occur after every spontaneous contraction. The increased variation during the deceleration is probably due to a more or less simultaneous increase of parasympathetic and ß-adrenergic activity. [7] Whether or not this is accompanied by hypoxic myocardial depression is

Fig. 3
Examples of a "decelerative" (A) and "terminal" (B) antepartum fetal heart rate pattern. Paperspeed 2 cm per minute.

unknown. With such a fetal heart rate pattern, baseline heart rate variation is about 5 beats minute and small accelerations may be observed. At elective Caesarean section, low arterial pO_2 and normal pH values will usually be found (Chapter 3). [15 44] With further deterioration, baseline variation will be reduced to less than 5 beats per minute with repeated late, mostly shallow decelerations: "the terminal heart rate pattern" (Fig. 3). [11 42 43] Accelerations have disappeared and fetal movements are absent. Sometimes a sinusoidal heart rate pattern can be observed. During these decelerations, heart rate variation is very low; this can probably be ascribed to hypoxic myocardial depression. This condition is strongly assocciated with fetal acidaemia and at elective Caesarean section, a pH in the umbilical artery of less than 7.15 has been found in the majority of cases. [44] If delivery does not occur in due course, fetal death will occur within one week.

Changes in fetal behaviour with progressive deterioration in the IUGR fetus

The subjective counting of fetal movements by the pregnant women ("kick charts") and the various kinds of objective recordings with mechanical, phonographic or piezo-electric devices have suggested that changes in the number of movements may distinguish the normal from the compromised fetus. [6 17 35] A sudden decline or cessation of maternally perceived movements has been found to precede fetal death by several days ("movement alarm signal"). [24] Other investigators have confirmed the association between a sudden cessation of fetal motility and intrauterine death. [28] Ultrasound data on the fetal motility of growth-retarded fetuses is limited. Roberts et al. (1978) have reported a reduction of fetal breathing and body movements. [31] In Chapter 3, we have described a reduction of fetal body movements below the normal range (5th percentile = about 5% of recording time) in 18 of the 27 IUGR fetuses with decelerative antenatal heart rate records. In IUGR fetuses without decelerations body movements were reduced below the norm in only one out of the 8 cases. With the assumption that the proces of deterioration is a continuum, it is speculated that the reduction of fetal body movements below the normal range occurs at about the same time as heart rate decelerations appear. This reduction is associated with fetal hypoxaemia. A decline in the incidence of fetal body movements must therefore also be considered as a late sign of fetal impairment. Furthermore, this indicates that quantitative analysis of fetal body movements before the development of heart rate abnormalities has limited practical importance. Only in the premature fetus with abnormal heart rate patterns quantitative analysis of fetal body movements might provide additional informatiori on the fetal condition. This is due to the fact that the interpretation of abnormal heart rate records between 26 and 32 weeks of gestation is difficult and that delivery is preferably delayed to gain maturation. In such cases a decline in fetal movements might identify a rapidly developing terminal situation. Fetal movements as perceived by the mother might also be useful in screening a total population. Daily fetal movement counting in a screenings program was found to reduce the incidence of antepartum fetal death. [22 25] Recently, however, in a large randomized study in 68.000 women no differences in antepartum death rates were observed, when formal counting was compared to informal noting of movements. [12]

As the incidence of fetal movements has appeared to be a rather insensitive discriminator of the fetus at risk, we have studied changes in the quality of distinct movement patterns (Chapter 6). This notion stems from investiga-

tions on low-risk and neurologically impaired preterm infants, in which a comparison of spontaneous motility revealed no differences in the quantity of specific motor patterns in both groups. [29] Yet, distinct changes in the quality of the different movement patterns could be recognized in the neurologically impaired infants. Studies on undernourished human infants and animal experiments have shown that in cases with growth restriction, the integrity of the nervous system is at risk or has already been impaired. [5 8] In Chapter 6 we compared motility in 10 growth-retarded and 10 normal fetuses to investigate whether the quality and quantity of motility in fetuses with impaired growth differed from well-nourished fetuses. The quality of the different movement patterns was studied extensively by replaying one hour video tape recordings. In the growth-retarded fetuses general movements were slow, lacking power and amplitude. They were characterized by a striking reduction in variability of intensity and speed of each movement, such that the normal waxing and waning of the movement disappeared. Although parameters such as speed, power and amplitude were reduced, the most impressive feature of the quality of movements was the overall monotony. Subtle movements of the arm and hand of varied speed and intensity were only seen in normal fetuses. Although this pattern was characteristic for the group as a whole, interindividual differences in performance existed. The qualitative analysis was performed by means of "gestalt perception" . In the computer era it is fashionable to underestimate the importance of such qualitative observations; yet, even if they are difficult to measure objectively, the visual "gestalt perception" appeared to be a powerful and sensitive instrument. The validity of this instrument was tested by 8 independant observers, who interpreted tapes of both normally and abnormally moving fetuses. A high level of overall interobserver agreement was found (89%) (Chapter 6). Other indications that changes in the quality of motor patterns may occur, can be found in studies by Sadovsky et al. [34 35 36] and Manning et al. [18] From subjective records kept by the pregnant women, Sadovsky et al. described a relative increase in the number of "weak" movements, together with a decrease in "strong" movements, preceding a reduction in the number of movements. [36] Using real-time ultrasound, Manning devised a scoring system for the detection of the fetus at risk: the "biophysical profile". One variable, "fetal tone" was assessed by the observation of the quality of a single limb movement. In normal fetuses, following extension of a limb, a rapid return to flexion was observed, whereas in compromised fetuses this did not occur. [18] The abnormal quality and reduced number of isolated arm movements and twitches found in the growth-retarded fetuses described in Chapter 6, confirm Manning's observations. However, it is questionable whether abnormal

"fetal tone" is the most appropriate description for the observed change in the quality of an isolated arm (or leg) movement. Our study on the quality of fetal motility in intrauterine growth retardation, was a cross-sectional one, which does not allow conclusions as to when these changes occur. Yet we speculate that these changes precede the reduction in movement incidence, which is supported by the large overlap in the incidence of movements in both groups.

From 36-38 weeks onwards, the normal fetus exhibits well- regulated fetal behavioural states with simultaneous changes in fetal heart rate, eye movements and body movements. [26] This is in contrast to growth-retarded term fetuses in whom a disturbance in behavioural state development has been described; especially the inability to synchronize the state variables at the transitions was evident. [2 49] As the fetuses from these studies had normal heart rate records, it is likely that impaired development of behavioural state precedes the occurrence of heart rate decelerations, just as qualitative changes in fetal motility do. This implies that these disturbances in fetal behaviour occur before the development of hypoxaemia; they cannot be attributed to impaired oxygenation.

Other indications that abnormal motor behaviour is not caused by hypoxaemia come from reports on growth-retarded newborn infants. These infants exhibited abnormal motor patterns, whereas the metabolic state was restored and adequate. [21 37] The common denominator in these growth-retarded fetuses cq. newborns, is the "reduced supply line". We therefore speculate that the chronic nutritional deprivation in growth retardation leads to impairment of neural development. This is supported by several animal and human studies, which indicate that intrauterine undernutrition can lead to reduced and defective neurocellular growth, myelinization or dendritic arborization. [5 8]

Changes in Doppler waveform patterns of the umbilical artery

Earlier signs of fetal impairment may be detected by Doppler recordings of umbilical artery or fetal aorta waveform patterns. Changes in these waveform patterns are thought to be indicative of increased vascular resistance: i.e. abnormal umbilical artery waveforms reflect increased vascular placental resistance. However, other explanations for the changes in waveform patterns, such as increase in blood viscosity or reduced arterial blood pressure, have not been excluded, as most studies concerned the "inaccessible" human fetus.

Reuwer et al. (1987) found a significantly raised pulsatility index (PI) of the umbilical artery at least 9 days prior to the occurrence of heart rate decelerations. [30] Other studies have also indicated that abnormal umbilical artery waveforms precede heart rate abnormalities. [1 33 41] In Chapter 7 the time relationship between the occurrence of abnormal umbilical artery waveforms and antepartum late heart rate decelerations, was studied in 70 growth-retarded fetuses. In 29 out of these fetuses longitudinal recordings were made and in 27 of the 29 fetuses (93%) abnormal PI values preceded the occurrence of decelerations. The median duration of the interval between the first abnormal PI value and the first heart rate deceleration was 17 days (range 0-60 days). This wide range indicates that Doppler recordings are of limited value for the timing of delivery. In some of the cases, decelerations occurred when umbilical artery waveform recordings were still normal. Normal waveforms cannot, therefore, be considered as definite proof of fetal well-being. In a large prospective study, Beattie and Dornan (1989) have assessed the usefulness of Doppler waveform analysis as an antenatal screening method for growth retardation. [4] They found low sensitivity and claimed that Doppler waveform analysis was of no value as an antenatal screening tool. Yet, using the 97th percentile as a threshold to define abnormal waveforms, they found a specificity of more than 95%. Using postnatal catch-up growth as a criterion for intrauterine growth retardation Van Vugt et al. (1988) found no clear relationship between umbilical artery waveform indices and growth retardation. However they indicated that increased PI values may identify a fetus with (subacute) distress. [50] This also suggests that it may be of use in a high risk population and substantiates the conclusion of Chapter 7 that abnormal umbilical artery waveforms are an indication for fetal (heart rate) monitoring.

Wladimiroff et al. (1986) have demonstrated a reduced pulsatility index in the internal carotid artery in growth-retarded fetuses, reflecting decreased vascular resistance in the fetal cerebrum. At the same time, the pulsatility index of the umbilical artery was increased, suggesting redistribution of cardiac output in favour of the brain, i.e. "brain-sparing" effect. [52] It would be interesting to know whether the aforementioned redistribution of fetal blood flow is associated with changes in heart rate and behavioural patterns or occurs at an earlier stage of utero-placental impairment. We speculate that the latter is the case.

Table 3
Neonatal neurological outcome in relation to antepartum fetal heart rate (FHR) patterns in small-for-dates (SFD) term and preterm fetuses.

	n	CS	pH_{ua} (mean)	Neonatal neurological diagnostic category			NNOS (median)
				Normal	Suspect	Abnormal	
SFD term fetuses							
Normal FHR	9	9	7.25	8	1	-	56
Decelerations	14	14	7.14	3	7	4	51.6
Total	23						
SFD preterm fetuses							
Normal FHR	12	-	7.18	7	5	-	53
Decelerative FHR	14	11	7.16	4	6	4	50.5
Terminal FHR	7	7	6.99	-	3	4	48.5
Total	33						

CS : caesarean section;
NNOS: neonatal neurological optimality score;
pH_{ua}: umbilical artery pH.

(From: Dijxhoorn, 1986)

Fetal heart rate and neonatal neurological morbidity

There are only a few studies on the relationship between antepartum fetal heart rate abnormalities and neonatal neurological outcome. Unfortunately all but one are impaired by the fact that part of the population was allowed to go into labour. This makes it difficult to determine whether outcome was related to antepartum complications or to problems induced by the process of labour or both. These publications have been summarized elsewhere.[47] In all the studies, a definite relationship was found between antepartum fetal heart rate abnormalities (decelerations) and neurological outcome. Data obtained from the Groningen Perinatal Project are shown in Table 3.[9] There was a strong correlation between heart rate decelerations (of which 80% occurred antenatally and the remainder in early labour) and neonatal neuro-

logical morbidity. Neurologically "abnormal" infants were restricted to the group with decelerations, with the poorest outcome in the subgroup with a "terminal" heart rate pattern. In the term group there was a good correlation between the umbilical artery pH and neurological morbidity. However, within the sub-group with decelerations no relationship with pH was found; these fetuses appeared to be more growth-retarded than those without heart rate decelerations. As abnormal neurological outcome was restricted to this sub-group, the significance of the actual pH at birth must be considered to be of limited value. [10] The same trend was present in the preterm group, in which all eight neonatal neurologically abnormal infants had abnormal (antepartum) heart rate patterns. Four of these infants had more or less normal umbilical artery pH values at birth (>7.15). These data indicate that the occurrence of antepartum decelerations is more important with respect to neurological outcome than the actual pH value at birth. [9]

As part of a follow-up study [13] all 33 preterm small-for-dates infants were re-examined neurologically at 4 to 6 years of age. Neurological abnormalities were found in two out of the seven with a terminal fetal heart rate, two out of the 14 with a decelerative pattern, whereas no abnormalities were found in the 12 infants with a normal antepartum cardiotocogram. [9]

In these studies from the Groningen Perinatal Project and other studies (see Visser 1988), a clear relationship was found between antepartum fetal heart rate decelerations and neurological morbidity. [47] This stresses the impact of prenatal hypoxaemia on the brain development of the growth-retarded fetus. Yet the behavioural abnormalities described in this thesis, suggest that impairment of neurological development occurs before hypoxaemia develops. In these growth-retarded fetuses with a "reduced supply line", brain damage is more likely to be due to chronic undernutrition (with superimposed hypoxaemia), than simply to hypoxaemia. Support for reasoning is rendered by the morphological findings in human growth-retarded infants and in animal models where a smaller brain size, fewer neurons, deficits in synapse-to-neurone ratios and reduced dendritic growth were found, rather than distinct, localized lesions. [5 8] In general, growth-retarded fetuses should be delivered before antepartum signs of hypoxaemia occur. Yet, as indicated above, this will not solve all the problems. Moreover, delivery at an earlier age might increase other (neonatal) risks. Research directed towards the prevention of growth retardation would seem to hold more promise with respect to the prevention of neurological handicaps, than further refinement of the assessment techniques for studying the fetal condition.

References

1. Arabin B, Siebert M, Jimenez E and Saling E. (1988): Obstetrical characteristics of the loss of end-diastolic velocities in the fetal aorta and/or umbilical artery using doppler ultrasound. Gynecol.Obstet.Invest. 25:173.

2. Arduini D, Rizzo G, Caforio L, Boccolini MR, Romanini C, Mancuso S. (1989): Behavioural state transitions in healthy and growth retarded fetuses. Early Hum. Dev. 19:155.

3. Barcroft J. (1947): Researches on Prenatal Life. Charles C. Thomas, Publisher. Springfield, Illinois.

4. Beattie RB, Dornan JC. (1989): Antenatal screening for intrauterine growth retardation with umbilical artery Doppler ultrasonography. Br. Med. J. 195.

5. Bedi KS. (1984): Effects of undernutrition on brain morphology: A critical review of methods and results. In: Current Topics in Research on Synapses Vol 2, pp 93-163. New York: Alan R. Liss Incorporation.

6. Colley N, Abraham NG, Fayers P, Talbert DG, Davies WL, Southall DP. (1986): The fetal phonogram: a measure of fetal activity. Lancet 1:931.

7. Court DJ, Parer JT. (1984): Experimental studies of fetal asphyxia and fetal heart rate interpretation. In: Research in Perinatal Medicine. Vol.1, Ed: Nathanielz PW. Perinatology Press, Ithaca, New York. p. 114.

8. Dobbing J. (1974): The later development of the brain and its vulnerability. In: Davis JA, Dobbing J (eds) Scientific Foundations of Paediatrics, pp 565-587. London: Heinemann.

9. Dijxhoorn MJ. (1986): Asphyxia at birth and neonatal neurological morbidity. PhD Thesis, University of Groningen.

10. Dijxhoorn MJ, Visser GHA, Touwen BCL, Huisjes HJ. (1987): Apgar score, meconium and acidaemia at birth in small-for-gestational age infants born at term, and their relation to neonatal neurological morbidity. Br.J.Obstet. Gynaecol. 94:873.

11. Emmen L, Huisjes, HJ, Aarnoudse JG, Visser GHA, Okken A. (1975): Antepartum diagnosis of the "terminal" fetal state by cardiotocography. Br.J.Obstet. Gynaecol. 82:353.

12. Grant A, Valentin L, Elbourne D, Alexander S. (1989): Routine formal fetal movement counting and the risk of antepartum late death in normally formed singletons. Lancet 2/8659:345.

13. Hadders-Algra M. (1987): Correlates of brain dysfunction in children; a follow-up study. PhD thesis, University of Groningen.

14. Harding R, Poore ER, Cohen GL. (1981): The effect of brief episodes of diminished uterine bloodflow on breathing movements, sleep states and heart rate in fetal sheep. J. Develop. Physiol. 3:231.

15. Henson GL, Dawes GS, Redman CWG. (1983): Antenatal fetal heart-rate variability in relation to fetal acid-base status at Caesarean section, Br.J.Obstet.Gynaecol 90:516.

16. Itskovitz J, Goetzman BW, Rudolph AM. (1982): The mechanism of late deceleration of the heart rate and it's relationship to oxygenation in normoxic and chronically hypoxemic fetal lambs. Am.J.Obstet.Gynecol. 142:66.

17. Jarvis GJ, MacDonald HN. (1979): Fetal movements in small-for-dates. Br.J.Obstet.Gynaecol. 86:724.

18. Manning FA, Baskett TF, Morrison I, Lange I. (1981): Fetal biophysical profile scoring: a prospective study in 1184 high-risk patients. Am.J.Obstet.Gynecol. 140:289.

19. Martin Jr. CB, van der Wildt, Slaitsch KJ, Jongsma HW. (1983): Intermittent reduction of uterine blood flow can modulate behavioural state in sheep. Washington DC: Society for Gynecologic Investigation, 30th annual meeting, March 17-20 :297.

20. Martin Jr. CB, de Haan J, van der Wildt B, Jongsma HW, Dieleman A, Arts THM. (1979): Mechanisms of late decelerations in the fetal heart rate. A study with autonomic blocking agents in fetal lambs. Eur.J.Obstet.Gynaecol.Reprod.Biol. 9:361.

21. Michaelis R, Schulte FJ, Nolte R. (1971): Motor-behaviour of small-for-gestational age infants. J.Pediatr. 76:208.

22. Moore TR, Piacquadio K. (1989): A prospective evaluation of fetal movement screening to reduce the incidence of antepartum fetal death. Am.J.Obstet.Gynecol. 160:1075.

23. Murata Y, Martin CB, Ikenone T, Hashimoto T, Taira S, Sagawa T, Sakata H. (1982): Fetal heart rate accelerations and late decelerations during the course of intra-uterine death in chronically catheterized rhesus monkeys. Am.J.Obstet.Gynecol. 144:218.

24. Myers RE, Mueller-Heubach E, Adamsons K. (1973): Predictability of the state of fetal oxygenation from a quantitatve analysis of components of late decelerations. Am.J.Obstet.Gynecol. 115:1083.

25. Neldam S. (1980): Fetal movements as an indicator of fetal well-being. Lancet 1:1222.

26. Nijhuis JG, Prechtl HFR, Martin Jr. CB, Bots RSGM. (1982): Are there behavioural states in the human fetus? Early Hum.Dev. 6:177.

27. Nicolaides KH, Campbell S, Bradley RJ, Bilardo CM, Soothill PW, Gibb D. (1987): Maternal oxygen therapy for intra-uterine growth retardation. Lancet i: 942.

28. Pearson JF, Weaver JB. (1976): Fetal activity and fetal well-being: an evaluation. Br.Med.J. I, 1305.

29. Prechtl HFR, Nolte R. (1984): Motor-behaviour of preterm infants.- In:Continuity of Neural Functions from Prenatal to Postnatal Life. Editor: Prechtl HFR, Clinics in Developmental Medicine. No94:79, Blackwell Scientific Publications Ltd, Oxford.

30. Reuwer PJHM, Sijmons EA, Rietman GW, Tiel Van MWM, Bruinse HW. (1987): Intrauterine growth retardation: prediction of perinatal distress by Doppler ultrasound. Lancet ii:415.

31. Roberts AB, Little D, Cooper D, Campbell S. (1978): Fetal activity in normal and abnormal pregnancies. Proc. 5th Fetal Breathing Conference, Nijmegen. Editor: Eskes TKAB University Press, Nijmegen. The Netherlands.

32. Robinson JS, Falconer J, Owens JA. (1985): Influence of growth retardation on functional capacity of fetal organ systems. Beard RW, Sharp F (eds) Preterm labour and its consequences pp 39-52. London: The Royal College of obstetricians and Gynecologists. ISBN 0902331337.

33. Rochelson B, Schulman H, Farmakides G, Bracero L, Ducey J, Fleischer A, Penny B, Winter D. (1987): The significance of absent enddiastolic velocity in umbilical artery velocity waveforms. Am.J.Obstet.Gynecol. 156:1213.

34. Sadovsky E, Yaffe H, Polishuk WZ. (1974): Fetal movement monitoring in normal and pathologic pregnancy. Int.J.Gynaecol.Obstet 12: 75.

35. Sadovsky E, Polishuk WZ, Yaffe H, Adler D, Pachys F, Mahler Y. (1977): Fetal movements recorder, use and indications. Int. J.Gynaecol.Obstet. 15:20.

36. Sadovsky E, Laufer N, Allen JW. (1979): The incidence of different types of fetal movements during pregnancy. Br.J.Obstet.Gynaecol. 86: 10.

37. Schulte FJ, Schremf G, Hinze G. (1971): Maternal toxemia, fetal malnutrition and motor behaviour in the newborn. Pediatrics 48:871.

38. Slikke Van Der JW. (1981): Antepartum Cardiotocografie. PhD Thesis. University of Amsterdam.

39. Smith JH, Anand KJS, Cotes PM, Dawes GS, Harkness RA, Howlett TA, Rees LH, Redman CWG. (1988): Antenatal fetal heart rate variation in relation to the respiratory and metabolic status of the compromised human fetus. Br.J.Obstet.Gynaecol. 95:980.

40. Snijders RJM, Ribbert LSM, Franssens M, Visser GHA. (1988): Heart rate variability in small-for-dates fetuses with abnormal umbilical artery velocity wave forms. Abstracts 3rd Int. Conf. on Fetal and Neonatal Physiological Measurements. Ed. K. Massal, Ronneby, Sweden, p. 87.

41. Trudinger BJ, Cook CM, Jones L, Giles WB. (1986): A comparison of fetal heart rate monitoring and umbilical artery waveforms in the recognition of fetal compromise. Br.J.Obstet.Gynecol. 93:171.

42. Tushuizen PBTh, Stoot JEGM, Ubachs JMH. (1974): Fetal heart rate monitoring of the dying fetus. Am.J.Obstet.Gynecol. 119:638.

43. Visser GHA, Huisjes HJ. (1977): Diagnostic value of the unstressed antepartum cardiotocogram. Br.J.Obstet.Gynaecol. 84:321.

44. Visser GHA, Redman CWG, Huisjes HJ, Turnbull AC. (1980): Nonstressed antepartum heart rate monitoring: implications of decelerations after spontaneous contractions. Am.J.Obstet.Gynecol.138:429.

45. Visser GHA, Heringa MP, Mulder EJH, Bekedam DJ. (1984): Effects of prolonged uterine contractions associated with fetal heart rate decelerations on human fetal behavioural states? (Abstract) In: Rolfe P, ed. Second Conference on Fetal and Neonatal Physiological Measurements. Oxford: Expres Litho Service p41.

46. Visser GHA. (1984): Antenatal cardiotocography in the evaluation of fetal well-being. Aust.NZ.J.Obstet Gynaecol. 24:80.

47. Visser GHA. (1988): Abnormal antepartum fetal heart rate patterns and subsequent handicap. In: Antenatal and perinatal causes of handicap. Ballière's Clin. Obstet. Gynaecol. 2/1, 117.

48. Visser GHA, Sadovsky G, Nicolaides KH. (1989): Antepartum heart rate patterns in small-for-gestational age third trimester fetuses: Correlations with blood gases obtained at cordocentesis. Am.J.Obstet.Gynecol. (in press).

49. Van Vliet MAT, Martin CB, Nijhuis JG, Prechtl HFR. (1985): Behavioural states in the growth retarded human fetus. Early Hum. Dev. 12: 183.

50. Van Vugt JMG, Ruissen KJ, Schouten HJA, Theunissen M, Hoogland HJ, de Haan J. (1988): Umbilical artery blood velocimetry: a prospective longitudinal study in search of the intrauterine growth retarded fetus. Early Hum.Dev. 18:59.

51. Wering JH. (1981) PhD Thesis: Transcutane pO_2-meting in de verloskunde. University of Amsterdam, p.103.

52. Wladimiroff JW, Tonge HM, Stewart PA. (1986): Doppler ultrasound assessment of cerebral blood flow in the human fetus. Br.J.Obstet.Gynaecol. 93:471.

SAMENVATTING

Zowel intrinsieke factoren (bv. genetische) als omgevingsfactoren kunnen er de oorzaak van zijn, dat een foetus in groei achterblijft, waardoor hij te licht is voor de duur van de zwangerschap. Tot de omgevingsfactoren behoort een tekortschieten van de materno-foetale uitwisseling van nutriënten en zuurstof. Afhankelijk van de ernst van het tekort kan dit leiden tot meer of minder ernstige intrauteriene groeivertraging en zelfs tot foetale sterfte.

Onderkenning van verminderde groei van de foetus is van belang, omdat onder die omstandigheden perinatale mortaliteit en morbiditeit verhoogd zijn . Voorts hebben ernstig in groei vertraagde (en veelal te vroeg geboren) neonaten een verhoogd risico op latere mentale en motorische ontwikkelingsstoornissen.

Dit proefschrift concentreert zich op de in groei vertraagde humane foetus, bij wie de reden van groeiachterstand waarschijnlijk een tekortschieten van materno-foetale uitwisseling betreft. Met niet-invasieve technieken, zoals registratie van het foetale hartfrequentiepatroon, echoscopische registratie van foetale bewegingen en Doppler-registratie van bloedstroomprofielen van de navelstrengarteriën, werd informatie verkregen omtrent het functioneren van het cardiovasculaire systeem en het centrale zenuwstelsel. Relaties met de actuele conditie van het kind werden onderzocht door vergelijking van deze registraties met de pH- en de bloedgaswaarden gemeten in navelstrengbloed verkregen bij electieve sectio Caesarea. Ook werden relaties tussen hartfrequentie- en bewegingspatronen en foetale oxygenatie "in vivo" bestudeerd. Enerzijds geschiedde dit door gebruik te maken van spontaan optredende momenten van foetale hypoxaemie ('late' decelerations van de foetale hartactie), anderzijds door het toedienen van extra zuurstof aan de zwangere en daarmee ook aan de foetus.

Dit onderzoek verschaft inzicht in veranderingen die optreden onder patho-fysiologische omstandigheden en leidt tot een nadere precisering van de betekenis van genoemde variabelen. Deze variabelen zijn verwerkt in een schema, waarin aangegeven wordt, wanneer zij afwijken van de norm bij verslechtering van de foetale conditie. Een dergelijk schema kan bruikbaar zijn voor de klinicus voor het bepalen van het tijdstip, waarop de in groei ver-

traagde foetus het beste geboren kan worden. Ook kan met een dergelijk schema de diagnostische betekenis van de verschillende technieken voor het bepalen van de foetale conditie geëvalueerd worden.

Na de inleiding en vraagstelling (hoofdstuk 1) wordt in hoofdstuk 2 de normale ontwikkeling van foetale hartactie- en bewegingspatronen in ongecompliceerd verlopen zwangerschappen beschreven. Kennis van normale patronen is essentieel voor het interpreteren van gegevens verkregen onder patho-fysiologische omstandigheden.

In hoofdstuk 3 wordt een onderzoek beschreven, waarin bij 37 in groei vertraagde foetussen het hartfrequentiepatroon en de incidentie van foetale lichaamsbewegingen gecorreleerd worden aan pH- en bloedgaswaarden uit navelstrengbloed verkregen bij electieve sectio Caesarea. Late decelerations van de foetale hartactie blijken indicatief voor het bestaan van foetale hypoxaemie. Zulke decelerations gaan in het algemeen samen met een tot onder de norm verlaagde hartactie variabiliteit. Ook de incidentie van bewegingen is dan abnormaal laag. Zijn er geen decelerations, dan zijn bovengenoemde variabelen meestal ook normaal. Geconcludeerd wordt, dat het foetale hartactiepatroon en de incidentie van bewegingen waarschijnlijk pas van de norm gaan afwijken bij het ontstaan van foetale hypoxaemie. Eén en ander gaat gepaard met het verschijnen van zogenaamde 'late' (hartaktie-) decelerations.

In de hoofdstukken 4 en 5 wordt nader ingegaan op de relatie tussen hartactie-variabiliteit en bewegingsincidentie enerzijds en foetale oxygenatie anderzijds, waarbij late decelerations van de foetale hartfrequentie worden opgevat als hypoxaemische momenten. Bestudering van de hartactie-variabiliteit alsmede van de incidentie van foetale adem- en lichaamsbewegingen voor, tijdens en na deze hartactie-decelerations verschaft informatie over het effect van "acute" hypoxaemie op deze variabelen. Bij 14 in groei vertraagde foetussen werd de invloed van een dergelijk "natuurlijk" hypoxaemisch moment bestudeerd (hoofdstuk 4). Zowel het aantal adem- als het aantal lichaamsbewegingen verminderde sterk tijdens late decelerations en de eerste 5 minuten nadien. Ook de hartactie-variabiliteit was de eerste 5 minuten na de deceleratie significant verlaagd. Dit suggereert dat hypoxaemie de hartactie-variabiliteit en de foetale adem- en lichaamsbewegingen onderdrukt.

In hoofdstuk 5 wordt een experiment beschreven, waarin bestudeerd werd of bij in groei vertraagde foetussen toediening van zuurstof aan de moeder (en daarmee ook aan de foetus) de suppressie van foetale adem- en lichaamsbewegingen teniet kan doen. Dit bleek inderdaad het geval te zijn. Ook de hartactie-variabiliteit nam toe tijdens O_2- toediening. Deze bevindin-

gen zijn in overeenstemming met de hypothese dat suppressie van foetale adem- en lichaamsbewegingen en van hartactie-variabiliteit onder meer het gevolg zijn van foetale hypoxaemie.

In hoofdstuk 6 wordt een onderzoek beschreven waarin naast de kwantiteit van diverse bewegingspatronen ook de kwaliteit ervan werd bestudeerd. Bewegingspatronen van in groei vertraagde foetussen werden vergeleken met die van foetussen met een normale groei. Als instrument voor de bestudering van de kwaliteit van foetale motoriek werd gebruik gemaakt van de zogenaamde "Gestalt perceptie". De validiteit van dit instrument werd onderzocht en er werd een goede "interobserver agreement" gevonden (89%). Hoewel de in groei vertraagde foetussen minder bewogen, waren het vooral de kwalitatieve veranderingen in de motoriek die opvielen. Terwijl bij de controlegroep de algemene lichaamsbewegingen gecoördineerd waren met variatie in kracht, snelheid en amplitude, waren deze bewegingen bij de groei vertraagde foetussen langzaam en uitgesproken monotoon. Ook de variatie in snelheid en intensiteit waren afgenomen. Verondersteld wordt, dat deze afwijkende motoriek van groeivertraagde foetussen het gevolg is van een verstoorde ontwikkeling van het centrale zenuwstelsel ten gevolge van chronische ondervoeding en hypoxaemie.

In hoofdstuk 7 wordt de tijdsrelatie tussen het optreden van afwijkende Doppler-bloedstroomprofielen van de arteriae umbilicalis en van late hartactie-decelerations antepartum beschreven. Van Doppler-stroomprofielen wordt verondersteld, dat ze een maat vormen voor de weerstand van het achterliggende vaatbed. Bij foetussen, die late hartactie-decelerations ontwikkelden, bleken de Doppler-metingen gemiddeld reeds twee en een halve week afwijkend. De spreiding in tijd was echter zeer groot (0-60 dagen). Geconcludeerd wordt dat afwijkende Doppler-profielen een indicatie vormen tot stringente foetale bewaking; door hun in tijd variabel moment van optreden kunnen ze - zeker tijdens de 'premature' periode - niet gebruikt worden om te besluiten de foetus geboren te laten worden.

In het laatste hoofdstuk worden de eigen bevindingen geïntegreerd met die van anderen. Een schema wordt gepresenteerd, waarin in tijd de veranderingen worden aangegeven, die optreden in Doppler bloedstroomprofielen en in hartaktie- en bewegingspatronen bij progressieve verslechtering van de conditie van de in groei vertraagde foetus. Geconcludeerd wordt, dat de meest gangbare antepartum foetale bewakingstechnieken pas in een vrij laat stadium aangeven, dat er sprake is van foetale bedreiging, namelijk bij het ontstaan van foetale hypoxaemie. De initiële daling van hartactie-variabiliteit en bewegingsincidentie zijn waarschijnlijk direct gerelateerd aan foetale hypoxaemie.

Foetale groeivertraging gaat gepaard met een verhoogde morbiditeit en mortaliteit. Het is onwaarschijnlijk, dat een verdere verfijning van technieken, waarmee antepartum de foetale conditie vastgesteld kan worden, zal leiden tot een aanzienlijke vermindering van deze morbiditeit en mortaliteit. Preventie van groeivertraging behoeft dan ook de aandacht.

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Is that all there is, my friend?
Well, lets keep on dancing.